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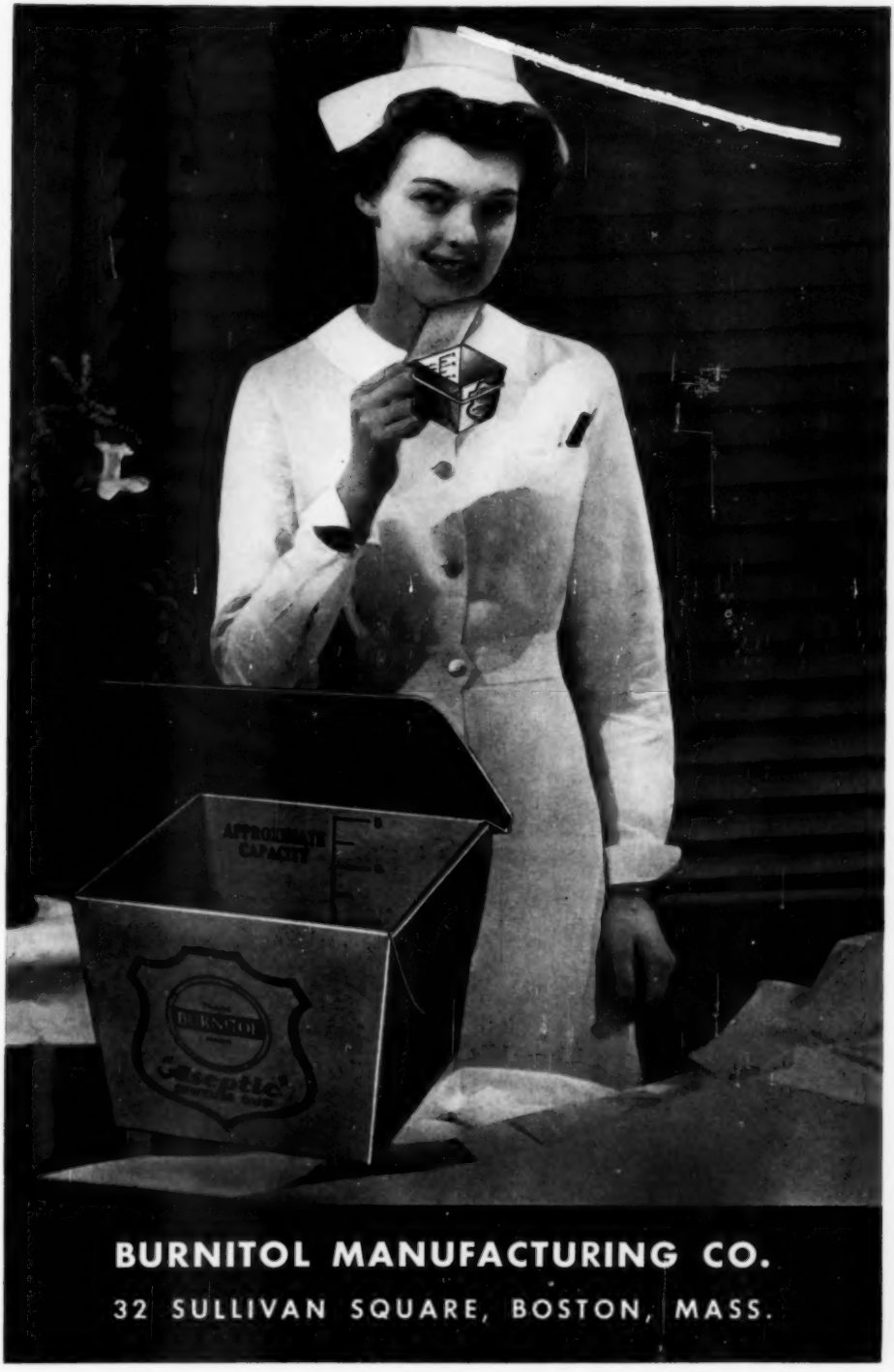

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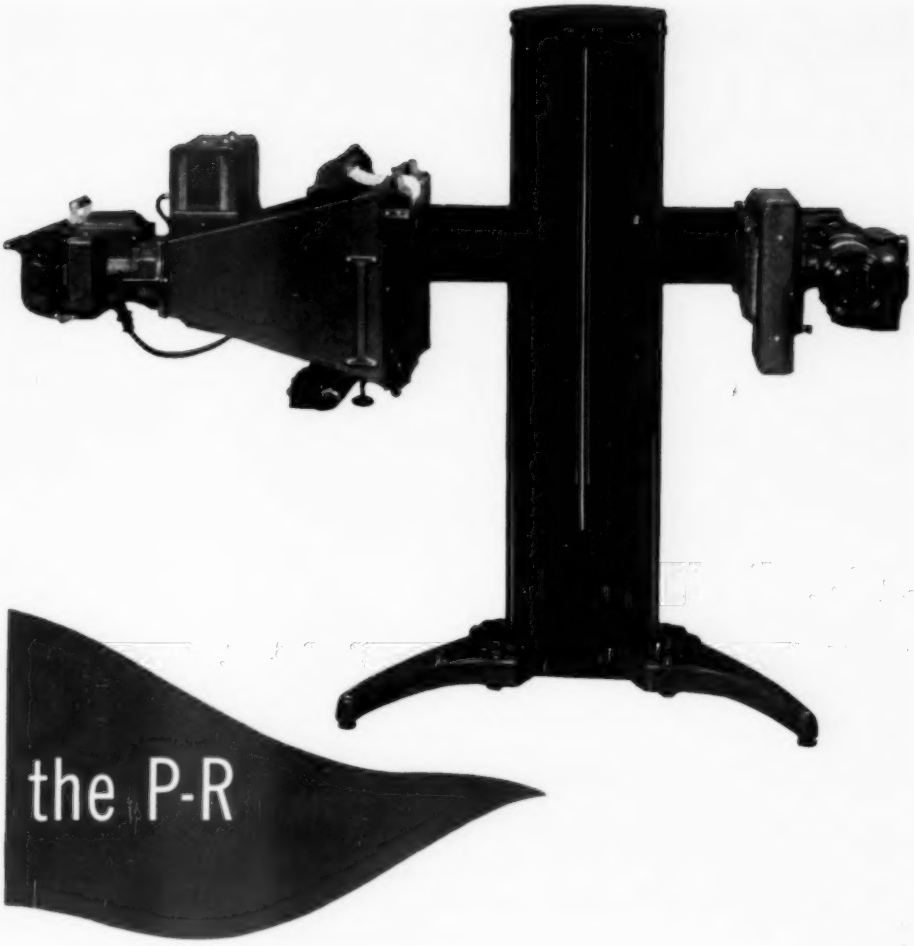

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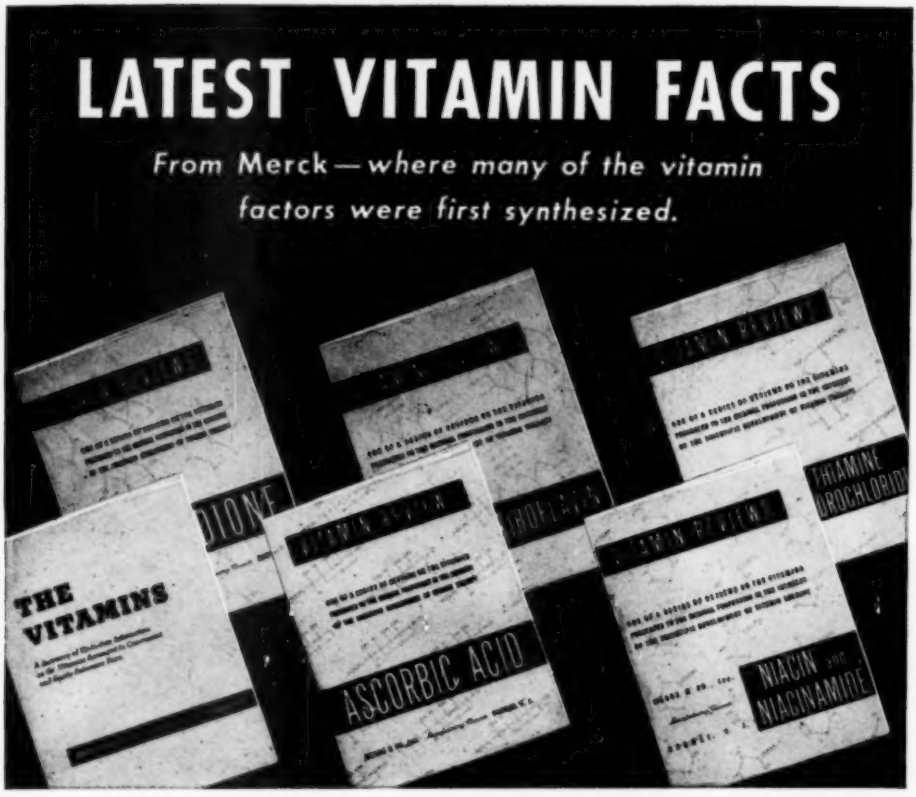

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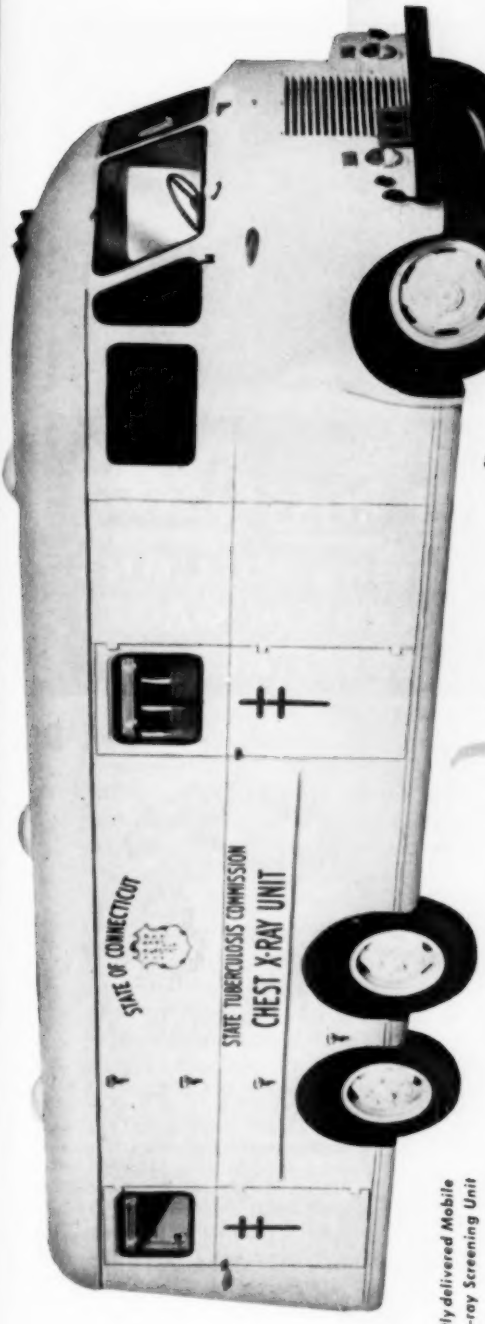

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CHEMOTHERAPEUTIC MEASURES IN TUBERCULOSIS: GENERAL ASSESSMENT AND CURRENT PROBLEMS[1]

P. D'ARCY HART[2]

HISTORICAL BACKGROUND

The ever widening field in which chemotherapy has achieved clinical success leaves the hitherto resistant infective diseases in increasing prominence. Among these, tuberculosis stands out as the main killing disease of bacterial nature affecting the productive groups of the population. The door to success at last seems to be opening, however, for in the past ten years clinical evidence of the value of a few substances has appeared. A number of others show promise. Let us, by way of introduction, take a brief look at the lines along which some of the researches have been traveling.

Present day developments with synthetic chemical agents date from the observation in 1938 by Rich and Follis (1) in Baltimore, that experimental tuberculosis in the guinea pig could be retarded by sulfanilamide. Trial of this sulfonamide in tuberculosis was a logical consequence of the historic discovery in Europe four years previously that the drug exerted an appreciable effect in acute bacterial infections. Workers at the Pasteur Institute in Paris (2, 3) soon demonstrated the more impressive anti-tuberculous activity of the related sulfone compounds, and this series has been developed and exploited in many countries since 1939.

Effective study of therapy with antibiotic substances, *i.e.*, with antimicrobial substances produced by species of living microorganisms, dates only from the introduction of penicillin as a chemotherapeutic agent in 1940. This great advance, by encouraging intensive study of other soil microorganisms, led Waksman and his colleagues (4) in New Jersey to the isolation of streptomycin in 1944. This drug has been given more experimental and clinical trial in tuberculosis than has any other product of microbial origin. A recent general bibliography of streptomycin (5) lists no less than 263 papers having a bearing on tuberculosis.

The development of the use of calciferol (vitamin D_2) in massive doses in lupus vulgaris has historical links with the treatment with enormous doses of cod liver oil given a century ago for many kinds of tuberculosis and for lupus (6). Moreover, the use of calciferol is linked also with heliotherapy in lupus insofar as this stimulus marshals the body's resources of vitamin D. Treatment with calciferol was introduced independently, and perhaps empirically, during World War II by Charpy (7) in France and by Dowling and Thomas (8) in England. Calciferol is not antibacterial in the sense of most chemotherapeutic agents but probably acts on the tissues of the host.

[1] Presented before the Medical and Public Health Sections, as part of the symposium on *Some Unmet Needs in Tuberculosis Control*, at the 44th annual meeting of the National Tuberculosis Association, New York, New York, June 18, 1948.

[2] Member of Scientific Staff, Medical Research Council, Great Britain.

Quite different was the mode of origin of the use of the synthetic substance para-aminosalicylic acid (PAS) which was introduced in Sweden in 1946 by Lehmann (9). The development of the drug resulted from knowledge of the metabolism of the tubercle bacillus that had accumulated during the previous decade, notably as a result of Bernheim's (10, 11) work in America.

These four chemotherapeutic agents or groups of agents illustrate both the diversity of approach of research to this problem and, in a wider sense, the internationality of medical science. With their mention we have all but covered the few substances that have already shown evidence of usefulness in tuberculosis, or are "in the running." I shall return to their assessment later.

RECENTLY REPORTED SUBSTANCES ACTIVE AGAINST MYCOBACTERIUM TUBERCULOSIS

In 1946 I had occasion (12) to tabulate the various substances reported to be active against the tubercle bacillus in the test tube or against tuberculous infection in the animal body. During the past two years the list has grown formidably. There is no need to present a survey of the subject in full, in view of several recent authoritative reviews (13 to 17), but we must consider what has been the positive yield from all these researches. Most of the substances studied have not been tested for antituberculous activity except in the test tube. Some have proved to be too toxic; others are inactivated in the body; and still others, particularly the antibiotics, may not yet have reached a stage suitable for animal experimentation because of problems related to purification.

In table 1 may be seen a summary of most of the substances or groups of substances reported to have some degree of antituberculous activity on the basis of recent tests in experimental tuberculous infection in animals, or in clinical tuberculosis in man.

Examples will be noted of purely synthetic substances, *e.g.*, promizole at one extreme, and products of biological origin, *e.g.*, streptomycin, at the other. The successes in animal experimentation number not much more than a score, those claimed or proved in man, half a dozen. An attempt will be made to assess these latter individually and very briefly.

ASSESSMENT OF CHEMOTHERAPEUTIC SUCCESSES CLAIMED IN MAN

Several hundred *sulfone-compounds* have been tested in the laboratory and the more promising of these have been studied in man. The latter include two of rather low toxicity, promizole (12 and 21), and the recently introduced sulfetrone (22, 77). It is a fair statement to say that the clinical results, while indicating some regressive effect, *e.g.*, in acute miliary tuberculosis (27) and in certain types of pulmonary tuberculosis (28–30), have not so far fulfilled the promise of the animal experiments *when these agents have been used alone.* Hinshaw and Feldman's (78) statement in 1945 that, as sole medicaments, "no definite place has been found for these drugs in treatment of the usual types of tuberculosis" seems still to be true. In combination with streptomycin therapy, however, the outlook is considerably more promising. Encouraging results have been reported in meningitis cases treated with promizole and

TABLE 1

Substances reported as antituberculous in vivo (1938 to 1948)

EXPERIMENTAL ANIMALS		MAN
(a) *Sulfonamides and sulfone compounds*		
Sulfanilamide (1, 18 and see 19)		
Other sulfonamides (20)		
Promin (see 12, 19, 21)		
Diazone (see 12 and 21)		
Promizole (see 12 and 21)		Promizole (26, 27; and see 12 and 21)
Sulfetrone (22)		Sulfetrone (28 to 31)
Other sulfones (23 to 25; and see 12)		Other sulfones (32, 33)
(b) *Fatty acids and derivatives*		
Ethyl palmitate and stearate (34)		
Certain chaulmoogra derivatives (35)		
(c) *Aromatic compounds*		
Certain naphthoquinone derivatives (36, 37)		
1-diethylamino 2-(2,4,6-triiodophenoxy)-ethane HCl (38)		
Para-aminosalicylic acid (39 to 43)		*Para*-aminosalicylic acid (44 to 47)
Thymol (48, 49)		
1,1,1-trichloro-2,2-bis (*P*-aminophenyl)-ethane (50, 51)		
2-butoxy-6-aminobenzothiazole HCl (52)		
Certain diaminomethylpyrimidines and related compounds (53, 54)		
(d) *Miscellaneous organic compounds*		
Nicotinamide (104, 105)		
Amido-compounds of α-furancarbonic acid (55)		
P-acetamidobenzaldehyde thiosemicarbazone (56)		*P*-acetamidobenzaldehyde thiosemicarbazone (106)
Ergosterol and related compounds (57, 58)*		Calciferol (7, 8, 59 to 63)
(e) *Antibiotics, etc.*		
Streptomycin (see 17, 21, 64)	Actinomycetes	Streptomycin (66 to 70, 100)
Mannosidostreptomycin (65)	Actinomycetes	
Chloromycetin (102)	Actinomycetes	
Subtilin (71, but see 72 and 107)	Bacteria	
Licheniformin (73)	Bacteria	
Nisin (74)	Bacteria	
Cepheranthine (see 75)*	Higher plants	Cepheranthine (see 75)
Usnic acid (76)	Higher plants	

* W. H. Feldman and A. G. Karlson, in unpublished studies, have failed to confirm the observations of others that either ergosterol (nonactivated) or cepheranthine is an antituberculous agent in experimentally infected guinea pigs (Personal communication, W. H. Feldman).

streptomycin simultaneously (26) and further trials of combined therapy are in progress in many countries.

Clinical trials of *para-aminosalicylic acid* (*PAS*) have been in progress in Sweden for two years (44, 47) and have been recently started in England (45, 46), in the United States and elsewhere. Yet, from reading the few papers so far published it is difficult to come to a firm conclusion on the efficacy of this drug in human pulmonary tuberculosis, or even in tuberculous empyema where apparently dramatic results may occur. Reports on the use of the drug in the treatment of meningitis are meagre. PAS is difficult and expensive to manufacture, and the early preparations were less satisfactory and more toxic than some in use at present. With the increased availability of satisfactory preparations of the drug, the wider trials now taking place should give an answer, provided they are properly designed. The administration of PAS, both alone and in combination with streptomycin, has been followed by significant changes in the course of experimental tuberculosis in the hands of some workers (23, 39, 42, 43), though not of all (41). There is no doubt that this interesting substance requires thorough examination in the field.

The dramatic and consistent improvements taking place under *calciferol* therapy (62) leave no doubt as to its efficacy in lupus vulgaris and certain other forms of skin tuberculosis. In tuberculous adenitis and possibly other non-pulmonary tuberculous conditions, suggestive results have also been obtained though the benefit is not clearly proved. In pulmonary tuberculosis the evidence for the efficacy of calciferol is very doubtful.

The Japanese (see 75) have claimed that the administration of minute doses of the alkaloid *cepheranthine* has resulted in improvement in many types of clinical tuberculosis. This drug is mentioned here only because the claims are so strong although well documented evidence is still awaited.

The discovery of *streptomycin* was of historic importance, not only because it was tuberculostatic in the test-tube, for many other substances have this property though not often to the same degree, but because of its low toxicity which permitted its use in effective doses in animals and man. The successful results observed with the streptomycin treatment of experimental tuberculous infections in guinea pigs (79) heralded the first real advance in the long struggle against this disease. Moreover, these results revealed the error of the ideas previously held by many that, in order for the chemotherapy of tuberculosis to be successful, it would be necessary to overcome the obstacle of the supposed fatty coat of the tubercle bacillus (streptomycin is water-soluble yet apparently passes readily into the cell).

The present status of streptomycin therapy in human tuberculosis has been succinctly described in various American reports, including that of the American Trudeau Society (66 to 69, 80). It is sufficient to state here that British Medical Research Council trials confirm the immediate life saving power of this antibiotic in a proportion of cases of tuberculous meningitis (70, 81) and acute miliary tuberculosis. Like the American workers, we have also found that streptomycin retards further progression and causes rather swift regression of

that element of pulmonary tuberculosis that is variously called infiltrative, exudative or bronchopneumonic. The striking improvements in some cases of ulcerative tuberculous laryngitis and tracheobronchitis following streptomycin therapy are sufficiently well known to require no further comment.[3]

SOME DEFECTS OF PRESENT ANTITUBERCULOUS AGENTS

Consideration will now be given to certain failures to meet the requirements for a satisfactory chemotherapeutic agent revealed by clinical trial of the various antituberculous substances.

A most important defect is toxicity. While the toxicity of streptomycin is remarkably low when considered in relation to effective dose, it nevertheless constitutes a problem. The permanent damage to the vestibular apparatus, even though it may be compensated for to some extent, provides a sound reason for the view that streptomycin is at present usually contraindicated in minimal pulmonary tuberculosis and in those other forms of the disease which may be satisfactorily treated by other measures. PAS can be given by mouth and seems to have little toxicity in man in the dosage used at present, but its efficacy is still *sub judice*. The sulfone drugs produce toxic blood changes to a varying degree, though these are comparatively slight with some of the newer products, particularly when administered by the parenteral route. The goitrogenic activity of the compounds, though again slight in some, is a distinct disadvantage. Massive doses of calciferol not uncommonly produce toxic effects, but these are seldom of sufficient severity to contraindicate the use of the drug.

Another and notorious bugbear of certain antituberculous agents, particularly streptomycin, is the phenomenon of the appearance of drug-resistant strains of bacilli. In the case of streptomycin, drug-resistant strains are frequently demonstrable after a month or more of treatment. It is of interest that this phenomenon seems to occur much less frequently in the course of meningitis than in pulmonary tuberculosis. If the great majority of the infecting bacilli cease to be susceptible to the drug, the curve of the patient's progress may flatten out after an initial improvement. Likewise, a patient may do well at first under streptomycin therapy but, if the disease flares up, say a year or more later, it may then be insusceptible to the drug. Consequently another reason against indiscriminate use of streptomycin in minimal disease amenable to ordinary treatment is the fear of spoiling the patient's chances for successful chemotherapy in the event of a subsequent relapse. From the community standpoint there is also a danger that new cases of tuberculosis will arise from contact with persons previously treated with streptomycin and who are discharging drug-resistant bacilli. The bacilli in such secondary cases might be

[3] A further group of compounds should be included under the heading or recent chemotherapeutic successes claimed in man. With the sulfonamides as starting point, Domagk and his collaborators in Germany have branched off on a new line, resulting in active thiosemicarbazones (56). Two of these, *p*-acetamidobenzaldehyde thiosemicarbazone and anisaldehyde thiosemicarbazone, have been given clinical trial, benefit in lupus vulgaris being claimed (106).

streptomycin-resistant from the very beginning of the infection and hence the disease would not be affected by streptomycin therapy.

The toxicity problem is being attacked in a number of ways. The most obvious approach is to synthesize new substances and to continue the search for fresh antibiotics. Attempts are being made to alter the chemical constitution of certain of the antituberculous antibiotics, including those that have not progressed beyond animal experimentation, in the hope of reducing toxicity more than antimicrobial activity.[4] It is possible that the same end may eventually be achieved by the synthesis of analogues of the simpler of the antibiotics. Reduction of the toxic effects of streptomycin is being attempted in the field by various modifications of the dosage schedule, as in current trials sponsored by the National Institute of Health and by the use of streptomycin in conjunction with other drugs, *e.g.*, the sulfones or PAS, in order to reduce the required dosage of the antibiotic. The results of animal experimentation (23, 43, 82, 83 and see 73 and 84) suggest that both of these lines of investigation have promise.

Various approaches are also being explored towards prevention of the baffling phenomenon of the emergence of drug-resistant strains of bacteria under streptomycin treatment. The attempts include variations in the schedules of administration to see if the emergence to predominance of drug-resistant bacilli can be delayed or prevented. The administration of streptomycin in conjunction with other chemotherapeutic agents may influence the phenomenon of drug-resistance, although a few results of simultaneous clinical use of sulfetrone and streptomycin (31) have not been encouraging. It would indeed be useful to have another drug to bring into action after the emergence of bacilli resistant to streptomycin. On the other hand, the fact that, in our experience, some cases of pulmonary tuberculosis continue to improve, even when resistance to streptomycin has apparently developed, may indicate that an important proportion of the bacilli are still sensitive (85). It is equally possible, however, that such improvement represents an effect of the patient's own resistance after the action of the streptomycin has ceased (86).

Defects other than those just mentioned are associated with one or more of the antituberculous agents under investigation at present. Caseous tissue seems to resist penetration by streptomycin, and pus is an unfavourable medium for its action, possibly on account of the depressive effect of an acid pH on an antibacterial drug of basic nature (87). This phenomenon may explain why the effects of streptomycin tend to be limited to the "exudative", bronchopneumonic elements of tuberculosis rather than the more chronic caseous elements, and why the drug is notably ineffective in tuberculous empyema. There is the possibility that PAS an acidic drug, does not possess these disadvantages.

In summary, it must be admitted that no single agent, not even streptomycin, has yet satisfied all the requirements for full chemotherapeutic success. The most important of these requirements are (88): (1) absence of serious or irreversible physiological derangements; (2) reversal of established progressive disease to nonprogression, resolution, fibrosis or calcification; (3) results to be

[4] This appears to have been achieved in the recent development of dihydrostreptomycin.

achieved in a reasonable period and to be lasting; (4) repeated use of the drug to be possible; and finally (5), a more questionable requirement, complete eradication of virulent infection. It would be foolish to assume that even combinations of current agents will entirely satisfy these criteria. Consequently, every new drug which appears to be suitable and safe for clinical application in tuberculosis must be submitted to the most grueling clinical-statistical assessment before it can be accepted or discarded. Otherwise, medical manpower and money may be culpably wasted to little purpose.

This problem of the assessment of efficacy of possible antituberculous agents is so pressing and so timely that most of the remainder of this lecture will be devoted to its discussion.

TECHNIQUES FOR THE ASSESSMENT OF ANTITUBERCULOUS AGENTS

Distinct advances in the laboratory methods for the testing of new antituberculosis remedies have been made over the methods of ten years ago. For *in vitro* assays we have improved media such as those of Youmans (25, 89, 90) and of Dubos and Davis (91), though it should be noted that the constituents of the latter medium may modify the chemotherapeutic action of some agents (92 to 94). For animal work we have the classical procedures of Feldman and Hinshaw (88) in guinea pigs and the introduction of mice for intravenous, intraperitoneal and inhalation infection (42, 73, 95 to 97).

In our techniques for assessing the value of new remedies in man, however, we are just emerging from the jungle of empiricism. Only a few months of enterprise sufficed to introduce tuberculin and gold into the treatment of tuberculosis on a world scale, despite inadequate early clinical trials. Nevertheless it took many years of scientific persistence to discredit these forms of therapy (12). It should be mentioned that untreated controls were rarely used for comparison in the early days of gold therapy and when they were used (particularly in one outstanding American trial (98)), the results were discouraging.

In spite of these and similar experiences, it is doubtful whether we have yet fully learned the lesson of how easy it is to ascribe to a new drug the improvement noted in a hotchpotch of tuberculous infections, without due regard to the possibility of remission from other causes. Even now, in the recent and current trials of the sulfones, streptomycin, PAS and other agents, can it be claimed that the selection of material, uniformity of treatment, and the basis of comparison for assessment of results, have always reached scientifically desirable levels? Moreover, now that experience with streptomycin has proved that drugs *can* influence human tuberculosis, there is a danger that the dearly won and healthy attitude of caution may be discarded and over-optimism and a too easy acceptance of newer measures take its place.

These considerations bring us to a key question in clinical trials, namely, under what circumstances is it necessary that a chance-selected, adequately matched group of untreated cases be studied concurrently with the cases receiving the particular treatment under investigation? If a drug prolongs life and produces apparent cure in a proportion of tuberculous infections of a type usually

associated with a one hundred per cent mortality, it is clearly evident that controls are unnecessary for evaluation of the therapy. Such a situation is provided by tuberculous meningitis and it is an interesting corollary that it is just in this and other acute fulminating forms of tuberculosis, which used to be said to constitute an unfair test of a chemotherapeutic agent, that the effect of streptomycin has been least equivocal. Untreated controls are also unnecessary where the course of the disease after administration of a drug is found to be in sharp conflict with previous clinical experience. In instances of this type there is such a prompt, rapid and easily observed reversal of the course of the infection that no doubt exists that a new factor is operating. Examples of this type of unequivocal therapeutic response are afforded by the early penicillin tests in acute pyogenic infections, and the course of tracheobronchial ulcerations or superficial sinuses after treatment with streptomycin. In the subacute and chronic tuberculous conditions, however, where improvement may characteristically occur either spontaneously or under the conventional methods of therapy, concurrent matched controls are desirable if the bias of the observer and extrinsic factors are to be excluded. For example, PAS introduced into the pleural cavity is apparently efficacious in clearing up certain tuberculous empyemata. It is possible that the observed results may represent a true effect of PAS. It is also possible, however, that the more vigorous or frequent aspiration or lavage likely to be associated with the chemotherapy *might* be the operative factor. Consequently the question cannot be answered unless controls treated similarly by aspiration or lavage alone are also studied. Likewise the effects of bed-rest must be taken into consideration in all chemotherapeutic trials in pulmonary tuberculosis.

Where provision of concurrent control cases is not considered feasible, it is necessary to have recourse to comparisons of the patient's progress under the chemotherapeutic treatment with one or more of the following: (a) with the disease trend in the same patient during a period of observation prior to treatment (for which purpose he would have to have been in bed for, say, at least two months); (b) with his expected progress had he not been treated with the drug, this being determined by independent experts on the basis of the pretreatment trend; (c) with the progress of a series of similar, but not drug-treated, cases taken from the hospital's records. These methods of comparison have been admirably used in certain investigations (66, 68) and have demonstrated the value of streptomycin *qualitatively* in a number of conditions. It is doubtful, however, if such methods can be used *quantitatively*. In order to make more precise evaluations and to answer the all important question, whether streptomycin is of *lasting* benefit in pulmonary tuberculosis, it is essential that "concurrent controls" be included. Another reason against using previous hospital records as a standard for comparison is the fact that the character of tuberculosis may change from year to year in a community, *e.g.*, with changes in the general nutritional level.

Concurrent controls have been used with good effect in explorations of the protective value of streptomycin in chest surgery. One of the projects in the

cooperative studies of the U. S. Veterans Administration, the Army, and the Navy (66) has been organized on such a basis. Controls have also been used to some extent in a test of streptomycin in pulmonary tuberculosis at Maybury Sanatorium, Michigan (99), and are a feature of the large scale cooperative trials of this drug in pulmonary tuberculosis recently started under the auspices of the Tuberculosis Study Section of the National Institute of Health. In controlled trials of this nature one can include heterogeneous types of the disease under study, provided that the total number of cases is sufficiently large to even out differences between treated and control groups. If this is not possible, the cases must be paired, which is a troublesome procedure. An alternative approach is to restrict the study to a homogeneous type of disease. Under such circumstances the numbers need not be so large for a comparability to be achieved between the treated and untreated groups, although the results will be more limited. Other conventional treatment can be added to both groups, or withheld from both. The second alternative is preferable scientifically but difficult to achieve in practice.

In Great Britain, extreme scarcity of supplies of streptomycin has up to the present prevented general distribution of the drug.[5] Although this scarcity has caused grave disquiet, it has had the advantage of providing time for the design and execution of certain controlled trials of the efficacy of the drug. In 1946, the British Medical Research Council was entrusted by the Ministry of Health with all the streptomycin that was available. In January, 1947, a number of trials in tuberculosis were started under the direction of the Council's Streptomycin in Tuberculosis Trials Committee, using 50 kg. of material imported from America. Two of the first studies will now be briefly discussed solely from the standpoint of technique of assessment.

One of the investigations was concerned with pulmonary tuberculosis. It was decided to choose a narrow and fairly homogeneous category, viz., bilateral, acute progressive tuberculosis of recent development in young adults, with expected bad prognosis and lesions which were unsuitable for collapse therapy. A number of specialist units were formed to cooperate with the Medical Research Council's central scientific staff who were to coordinate the work. The task of maintaining uniformity of the type of case under study was assigned to a central selection panel. The most important decision was that one-half of the cases selected were to be given streptomycin and one-half were to be studied in parallel as non-streptomycin-treated controls (though not in the same wards). Once a case had been selected for trial, the decision as to whether it was to be streptomycin-treated or to be a control was predetermined from a list of case numbers prepared by a statistician. A sealed envelope carrying the case number outside contained the decision, which was not known in advance even by the central staff. There was a common record sheet for the trial and a high degree of uniformity of procedures was obtained. The latter was helped by meetings of the clinicians and pathologists and by periodic visits of the central staff to

[5] A limited allocation of streptomycin for routine use has been made by the Ministry of Health to the Regional Hospital Boards since this talk was given.

the local units. It was agreed that other active treatment should be adopted only if the course of the disease so changed that it became indispensable and urgent, though every patient received bed-rest and all the usual dietetic and other symptomatic therapy. The group of investigators thus submitted itself to a considerable degree of self-discipline. It should be added that, in spite of the even chance of a case being made a control, there was every inducement for clinicians to submit their patients for this scheme, since no other practicable specific treatment and no other assured source of supply of streptomycin were then available.

This trial was completed by April, 1948, after four months' treatment and a total of six months' observation in bed of each case. The results are being analysed,[6] but preliminary tabulations show a contrast between the 55 streptomycin-treated cases and the 52 non-streptomycin-treated controls. The evaluation is based on the (provisional) percentages of improvement, of deterioration and of death, at four and at six months after the start of chemotherapy. The roentgenographic assessment was by three specialists who were unassociated with the trials and ignorant of the category of the patients and who read the films independently. Although the advantage is strikingly with the streptomycin-treated group, a proportion of the controls showed improvement, thus demonstrating the possible fallacies had a control group been omitted. Furthermore, the treated group tended to do best in the first four months while such improvement as occurred in the controls *i.e.*, without streptomycin, was usually much slower, a contrast that could hardly have been appreciated without the use of a control series. It is justifiable to conclude that this controlled trial has already yielded a clear short term result, albeit on one category of pulmonary tuberculosis and that a rather uncommon one. A long term comparative follow-up of the two groups (allowing for complications due to subsequent collapse therapy or other treatment) should add further information to this study. It should be emphasized that the use of non-streptomycin-treated controls was considered to be ethically justified in this particular trial for three reasons: (*1*) it was not possible to say with certainty that streptomycin would be advantageous; (*2*) the type of case selected was usually unsuitable for alternative active treatment; (*3*) all of the small supply of streptomycin available was being used for treatment.

The other of the British early trials of streptomycin was made in children with tuberculous meningitis and the results were published in April, 1948 (70). In this study a comparison of the fate of streptomycin-treated cases, according to duration of disease when chemotherapy was started, demonstrated the great advantage of early diagnosis and the consequent importance of concentrating limited supplies of the drug on such cases. An important comparison was undertaken to decide whether the irritating effects of intrathecal treatment could be avoided in meningitis by restricting administration of streptomycin to the intramuscular route. For this purpose, alternate cases admitted to the wards were treated by the intramuscular route alone or by combined therapy (changing from the former to the latter only if it became clear that the method

[6] A full report of this investigation has now been published (100).

was failing). The results of this inquiry answered the question decisively: combined therapy is essential and intramuscular administration alone is inadequate. Such an unequivocal answer could not have been achieved unless two series of cases had been studied in parallel under fairly uniform conditions. Evaluation of an accumulation of individual clinical experiences with a variety of types of tuberculous meningitis would have taken far longer and the conclusions would have been less definite. Moreover, although the present drastic procedure involved the loss of several lives, it will have saved many more if it serves to prevent future uncontrolled experimentation on these lines. The technique of assessment here again has been of prime importance.

Summarizing the position so far reached on techniques of evaluation, it may be stated that careful objective clinical assessment, based on previous experience with similar types of cases as a standard, should, with rigid safeguards, be adequate to demonstrate whether a new drug gives either benefit or no benefit, provided its action is more than slight. On the other hand, the inclusion of a matched control series, studied concurrently in order to permit comparisons having statistical validity, would seem imperative for a precise evaluation of a new drug's possibilities, limitations, and the degree of permanence of its benefit. Likewise, such control cases are necessary in studies of the part played by the patient's own resistance to the infection when under the drug treatment or after its discontinuation and to ascertain the best combinations of chemotherapy with the usual methods of local surgery, such as pneumothorax and thoracoplasty. It is hardly necessary to add that only for certain purposes need the control series in such investigations be untreated by the drug, as was the case in the British pulmonary trials described. In many instances, as with the meningitis series, the "controls" will receive the treatment but in a contrasting manner. It should be noted that some investigators might prefer to use another word for this application of the concept of a controlled study. Examples may be mentioned of specific problems which are capable of solution by parallel comparisons more rapidly than would otherwise be the case. One of these is the question of the optimum regimen of administration of streptomycin in meningitis. For instance, were the results in a recent series described by Dubois of Brussels (101) better than the results obtained in the British trials because of the long periods of rest from streptomycin treatment of any kind? Another question is how far prophylactic intrathecal treatment may prevent the complication of meningitis in cases of acute miliary tuberculosis.

A further point not yet generally appreciated is that the problem of the techniques for assessing new drugs in tuberculosis is in some ways more difficult now that we have in streptomycin an agent that is known to be decisive in certain conditions. For example, *assuming an adequate supply of streptomycin*, it is questionable whether it is ethically justifiable to withhold this drug and to substitute an unproved one in the treatment of tuberculous meningitis. It is more justifiable to give streptomycin alone in one such series and streptomycin plus the new drug in another, although assessment may well be confused under such circumstances. On the other hand, in certain types of pulmonary tuberculosis,

it might be ethically correct to study a drug-untreated control series, at least for a time, against the treated series, in order to obtain a first evaluation of the new drug. As an alternative system the new drug could be tested in comparison with streptomycin. Unquestionably this whole problem of investigation techniques will itself develop and change as new remedies grow in number and variety.

LOOKING AHEAD

I have tried in this talk to take stock of the status of antituberculosis chemotherapeutics in a general way and to discuss the technical equipment for the clinical assessment of individual drugs. The future needs of chemotherapy will be conditioned by the changing pattern of tuberculosis. There is no doubt that a prime objective will be a drug, a combination of drugs, or a technique of administration of drugs, for use in minimal pulmonary tuberculosis. In order for such a treatment to be satifactory, it must produce results rapidly, safely, and without appreciable risk of the emergence of drug-resistant infecting strains. The prospects for the development of treatments of this kind are reasonably good. The very variety of the promising chemotherapeutic agents already under examination is a good omen for the development of better ones, whether they be found through synthesis by the organic chemist or by Nature. Perhaps a number of such drugs will come to supplement or even to replace streptomycin, though this antibiotic will retain its place of honor in medical history.

Even should our hopes of successful chemotherapy be fulfilled, this weapon is still unlikely by itself to lead to the eradication of tuberculosis. For tuberculosis tends to be a chronic infection firmly implanted in the tissues, and chemotherapy must be considered as only a part of the complex of treatment that has been built up through the years. The importance of the contact factor and the contribution of the patient's inborn and acquired resistance to the infection, in other words the vital function of prevention in this fight against tuberculosis, must also be always borne in mind. In a study of statistics in large towns in England, the pulmonary tuberculosis mortality in young women was found to be nearly twice as high in the most overcrowded boroughs as in the least overcrowded and doubtless a similar relationship exists in this country. Thus in the control of tuberculosis the technique of living is as important as the technique of treatment.

Finally, let us never forget to regard tuberculosis as a world problem. This disease is perhaps being defeated in some parts of the world, but, while the death rate per 100,000 is 42 in New York City and 44 in Copenhagen, it is 132 in Glasgow, 135 in Rome and 275 in Warsaw. Moreover the Warsaw rate is nearly twice what it was before the destruction due to war. In the whole world there are perhaps some ten to twenty million sufferers from active tuberculosis. There is plenty of work to do. I believe that this meeting of key men and women will provide inspiration for us all to go forward in this task of peace.

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THORACOSCOPY AND CLOSED INTRAPLEURAL PNEUMONOLYSIS[1,2]

O. C. BRANTIGAN

INTRODUCTION

Although references to pneumothorax as a therapeutic procedure date back to antiquity, it became a generally popular method of treatment for pulmonary tuberculosis about 1910 (1). Since intrapleural adhesions often interfere with adequate pneumothorax collapse of the lung, it is natural that a method of freeing the lung from the effects of adhesions would be developed. Friedrich (2) probably did the first pneumonolysis in 1908. It was the open type of pneumonolysis. The closed method of releasing adhesions was developed by Jacobaeus and Beiter (3) in 1913 and, interestingly enough, the procedure had to prove its superiority over the open type of operation. In the beginning there was no real difference in the indications for the two operations. The closed method of intrapleural pneumonolysis became the accepted procedure in Europe before it did in the United States but by 1929 Matson (4) had established it in this country as the operation of choice for freeing intrapleural adhesions. By 1934 the open method of pneumonolysis had been rather generally discarded because the morbidity and the mortality were extremely high after the operation. In spite of the high mortality and morbidity, Anderson and Alexander (5), Dohnanyi (6), and Hoppe (7) maintained that the open method procedure, when properly used, had its place in the treatment of pulmonary tuberculosis. In 1946 the author (8) reported his experience with 15 patients who were subjected to the open type of pneumonolysis. Since that report the open method has been used on 8 additional patients. There have been no serious immediate or late postoperative complications and the end results have been gratifying. The introduction of new chemotherapeutic agents makes the operation even more desirable and probably will extend its use to include patients who have more extensive adhesions. It seems, however, that the other rigid indications should be maintained. The open type of operation should not be considered unless there is failure to free the lung by the closed method.

Since the work of Matson (4), the closed method of intrapleural pneumonolysis has been accepted without controversy. It has been ably supported by Moore (9), Goorwitch (10), Bayliss (11, 12), Kunstler (13), and others. There has, however, been considerable discussion concerning the efficiency of the one or two piece pneumonolysis instrument. There has also been much controversy as to the advantages or disadvantages of galvanocautery compared with high frequency electrosurgical cutting current (electrosurgery).

[1] From the Department of Surgery, School of Medicine, University of Maryland, Baltimore, Maryland.

[2] Presented before the Medical Section, as part of the symposium on *Surgery—Trends—Late Results*, at the 44th Annual Meeting of the National Tuberculosis Association, New York, New York, June 16, 1948.

OPERATIVE TECHNIQUE

It makes little difference whether there are one, two, or more trocar holes through the chest wall. The size of the trocar hole is unimportant, particularly when compared with an open incision into the pleural cavity. At the beginning of the operation the use of two cannulas permits the inspection of the pleural cavity from two different points of view. The adhesions may appear simple or impossible of release, depending upon the angle from which they are viewed. The two piece instrument eliminates the fixed position of the cutting instrument in the field of vision. Thus, a close-up view of the actual cutting can be obtained or in a moment the whole field of operation can be examined without interrupting the operation. After using both instruments, the two piece type is now employed exclusively.

Galvanocautery, or the electrosurgical cutting current, can be used as the cutting method with either the one or two piece pneumonolysis instrument. It is usually claimed that tissue destruction is greater with galvanocautery and that the separation of areas of necrosis may lead to secondary hemorrhage or spontaneous pneumothorax. Actually, the area of tissue destruction with either galvanocautery or electrosurgery depends upon the intensity of the heat in the former and the strength of the current in the latter. The extent of tissue destruction, therefore, depends more upon the individual operator than it does upon the method employed. Heat and smoke produced by galvanocautery properly employed are insignificant. The time consumed in completing an operation by either method depends upon the patient and the operator. Should brisk hemorrhage occur from a blood vessel that is less than one of the great vessels, it can be controlled more easily with the electrosurgical method. If hemorrhage can be controlled with electrosurgery, however, it also can be controlled with galvanocautery. In the event a great vessel is opened, neither method will control the hemorrhage. There is no electrical shock or muscle spasm from galvanocautery, and undoubtedly there will be none with electrosurgery if the apparatus is handled correctly. Since the galvanocautery is the simpler apparatus, mechanical failure probably will occur less frequently than with the electrosurgical unit. (After using both types of cutting instruments the galvanocautery is now used exclusively.) When operating with the galvanocautery equipment, an electrosurgical electrode could be made available for use in case of bleeding. It seems quite likely that an electrosurgical electrode would always be on hand if bleeding actually were troublesome when using galvanocautery.

The heat of the cautery or the strength of the electrosurgical cutting current must be regulated according to many factors since in using either method the tissues may be cut so quickly that bleeding occurs or so slowly that excessive charring results. In general, fibrous tissue, fatty tissue, and edematous tissue require a hotter cautery or a stronger cutting current. When holding the cutting instrument constantly in contact with the tissue or when attempting to keep a greater area of cutting surface against the tissue to be cut, a hotter cautery or a stronger cutting current is required. Should bleeding occur, it can be controlled easily by the electrosurgical method; if cautery is being used, however, it is often controlled most readily by reducing the heat below that used in operating. The cold electrode is placed firmly against the bleeding point and then the current is turned on. The cautery point is held in place until the tissue is charred. As the heat is reduced, it will not cut deeper into the tissue. If it cut deeper into the tissue, it might cause additional bleeding. The charred tissue will adhere to the cautery point. Therefore, when the point is to be removed, it must be done gently and with the heat of the cautery point increased. Bleeding often can be controlled adequately by the injection of a generous amount of procaine with epinephrine solution at the site of bleeding. The author has never observed bleeding from the lung side of a released adhesion.

All surgery that is accomplished though an eyepiece for vision remains concealed from onlookers or critics. The closed type of pneumonolysis is no exception and, as sterility must be carefully guarded, it is difficult, if not impossible, to photograph the operation. The actual operative technique, perhaps, will depend upon the individual operator. Nevertheless, certain aspects of the operative procedure should be discussed. After a patient who had undergone a closed pneumonolysis developed a pure *Staphylococcus albus* empyema, sterile hoodlike masks have been employed (figure 1). The operator wears glasses sterilized by soaking in alcohol (figure 1). The operation is always begun with the patient in the lateral position. A wide area of skin is prepared. Well within the cleaned skin area, procaine wheals are made in which towels can be anchored to the skin by towel clips. The towels are then placed so as to give access to an area of skin anteri-

FIG. 1. The photograph shows the operator dressed for closed pneumonolysis. He is wearing a sterile hood and sterile eyeglasses.

orly, laterally, and posteriorly. The towels are anchored to the skin so that they cannot shift as the patient is turned in various positions (figures 2 and 3). The first trocar and cannula puncture site is selected in about the third interspace at approximately the anterior axillary line (figures 4 and 5). Roentgenograms suggesting an adhesion in this region may cause a variation of the first puncture site. The second trocar and cannula puncture site is selected after adhesions have been thoroughly examined; usually it is inferior and posterior to the first cannula, just anterior to the inferior angle of the scapula. Care is exercised so that the second site selected is not too close to existing adhesions. It has been found that a cannula inserted posterior to the inferior angle of the scapula affords restricted motion of the instruments and accordingly is avoided except for an attack upon a selected adhesion. The two cannula sites are also selected so that the instruments can be manipulated in any one of the three usual positions that the patient may have to assume during the operation; supine, lateral, and prone (figures 4 and 5). More than two cannulas are inserted if necessary.

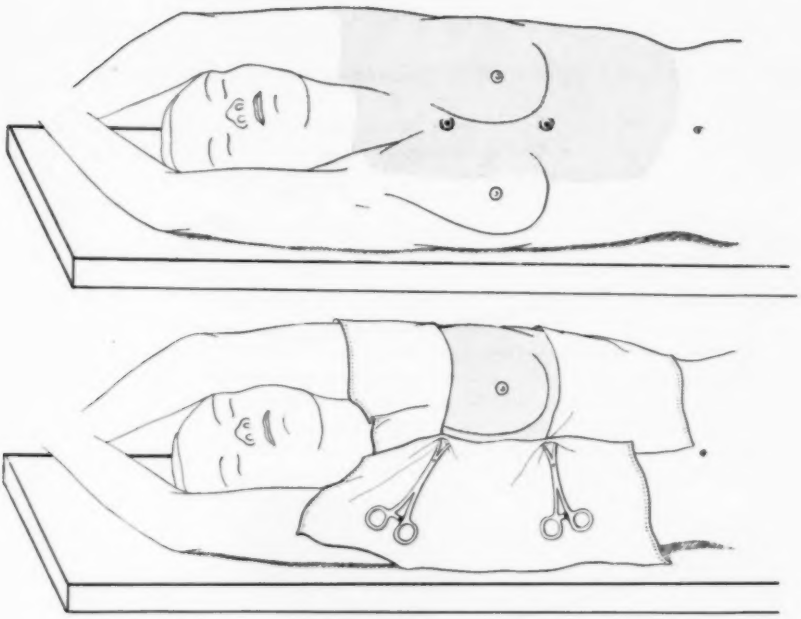


FIG. 2a. (Upper) An anterior view of the large area of skin prepared for operation. The procaine wheals may be seen.

b. (Lower) The method of draping the patient for operation is illustrated. The towels are anchored to the skin by towel clips inserted into the skin at the site of the procaine wheals.

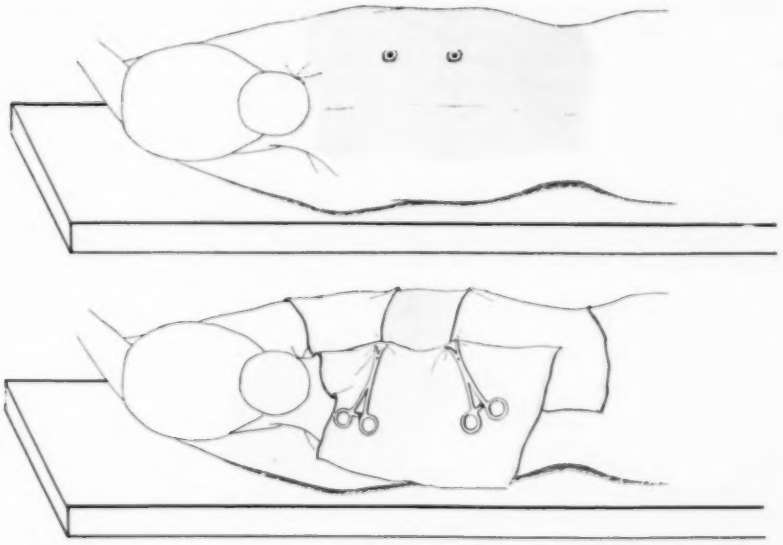
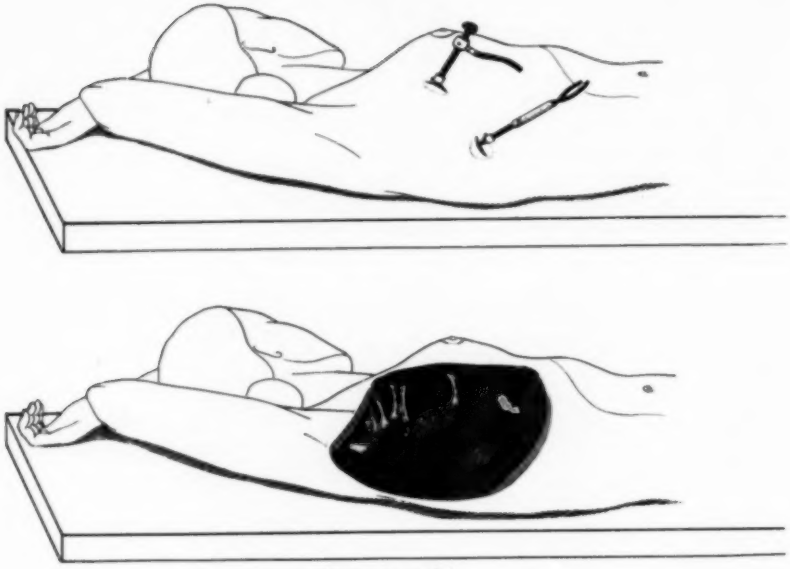
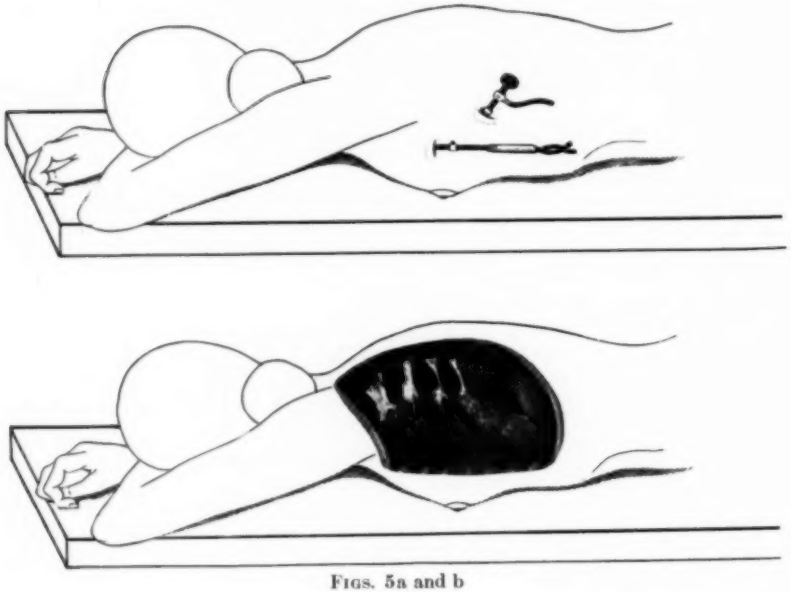


FIG. 3a. (Upper) A posterior view of the large area of skin prepared for operation. The procaine wheals may be seen.

b. (Lower) The method of draping the patient for operation is illustrated. The towels are anchored to the skin by towel clips inserted into the skin at the site of the procaine wheals.



FIGS. 4a and b



FIGS. 5a and b

As in the presence of a pneumothorax the lung falls by gravity, it is important to put the patient in a position that will cause the weight of the lung to pull upon or stretch the adhesion under surgical attack (figures 4 and 5). Therefore, the patient must be prepared and draped and the cannulas inserted in such a manner that he can be placed in any and all positions; head up, head down, prone, supine, lateral, and even at times with the patient so close to the edge of the operating table that the contralateral side of the chest is uppermost.

If the weight of the lung is allowed to pull upon or stretch the adhesion under surgical attack it can be released from the chest wall more easily and safely. As a portion of the adhesion is freed, it will fall away from the chest wall and permit better access to the remaining portion of the adhesion (figure 6). Bayliss (12) recommends insertion of a third cannula in order that traction can be made upon the adhesion under surgical attack. The writer has employed this method when for some other reason a third cannula has been necessary. The application of traction upon the adhesion under surgical attack, as Bayliss so adequately describes, is a most effective method and perhaps should be adopted as a routine procedure in closed intrapleural pneumonolysis.

Adhesions are removed from the chest wall as described by Carter (14): they should not be cut or divided. Even the simple adhesions are attacked in this manner for it keeps the operator in practice. The parietal pleura and endothoracic fascia are divided near the base of the adhesion and the adhesion is then released in the extra-endothoracic plane. This usually is an areolar tissue plane. The fascia covering the intercostal muscle can be recognized on the chest wall side (figure 6). In patients where pneumothorax has been of short duration, the plane is identified easily. The areolar tissue melts like butter ahead of the cautery and rarely is bleeding encountered. Small capillaries must be present since *cold stripping* causes enough bleeding to obscure the fine identification necessary to maintain the plane. Dissection in the extra-endothoracic fascial plane of areolar tissue with hot cautery has been so successful that the author completely gave up the cold stripping method (15, 16). In order to release adhesions in the extra-endothoracic fascial plane, it is necessary to have the adhesions on a stretch. This method of release of the adhesions is safe as one cannot injure the lung even though a portion of it is adherent to the chest wall. The intercostal vessels are separated from the plane by the internal intercostal muscle except posteriorly, where the posterior intercostal membrane replaces

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FIG. 4. The drawings illustrate the patient placed in the supine position on the operating table. The patient is placed close to the edge of the table.

a. (Upper) The pneumonolysis instruments are placed in a position that will allow manipulation in the supine, lateral, or prone position. The eyepiece and cautery can be used interchangeably in either cannula.

b. (Lower) The drawing shows that the lung falls by gravity to the posterior part of the chest. Adhesions from the anterior aspect of the lung to the anterior chest wall are placed on tension by the pull of the lung. An adhesion on tension is released more easily by closed pneumonolysis. If adhesions are present from the posterior aspect of the lung to the posterior chest wall they cannot be seen and hence could not be released.

FIG. 5. The patient is placed in the prone position on the operating table, close to the edge of the table. Sometimes the torso is extended over the edge of the table, thus permitting freer manipulation of the pneumonolysis instruments.

a. (Upper) The pneumonolysis instruments are in place as indicated in figure 4a.

b. (Lower) The drawing indicates the lung falling anteriorly by gravity. The posterior adhesions are placed on tension by the weight of the lung. Anterior adhesions cannot be seen and hence could not be released in this position.

the internal intercostal muscle. At this posterior location and anteriorly at the internal mammary vessels, both the veins and arteries are subpleural and vulnerable. In these locations extrapleural or extra-endothoracic fascial separation must be abandoned and the adhesion divided. When the adhesions are attached to the large blood vessels or to the trachea or esophagus, they must be divided, since release in the extrapleural or extra-endothoracic plane is dangerous if not impossible. The partial release or partial division of an individual adhesion is avoided when possible. On occasion, however, it is necessary

FIG. 6. The drawings illustrate the method of releasing adhesions by the closed type of pneumonolysis using galvanocautery. The patient is placed in a position that will cause tension on the adhesion. The weight of the lung pulls upon the adhesion.

a. (Left) The adhesion is first attacked by cutting through the pleura and endothoracic fascia approximately a centimeter away from the base of the adhesion.

b. (Centre) As the adhesion is released in the extra-endothoracic fascial plane the weight of the lung pulls the released portion of the adhesion away from the chest wall, allowing free access to the remaining portion of the adhesion. The extra-endothoracic fascial plane is areolar tissue, which melts like butter ahead of the hot cautery. In this plane bleeding does not occur unless the lung is stripped by the cold cautery. The internal intercostal muscle or the intercostal membrane usually can be identified without difficulty. If the adhesion is divided in its smallest part, injury to the lung parenchyma will occur if the lung parenchyma is drawn into the adhesion. When the adhesion is released in the extra-endothoracic fascial cleavage plane, the lung parenchyma cannot be injured even if the visceral and parietal pleura are intimately adherent.

c. (Right) The area of chest wall denuded is generally several times greater than the smallest part of the released adhesion.

to begin the release or division before the operator can be certain about his ability to completely release or divide the adhesion.

The objective of the operation is to free the lung completely from the chest wall, mediastinum, and even from the diaphragm. At one time it was thought that the duration of the operation was important but such reasoning has been discarded. The operation requires from twenty minutes to two and one-half hours. All adhesions are released if possible. There is never a deliberate plan to attempt to complete the freeing of the lung at a subsequent operation. Subsequent operations have been rather disappointing.

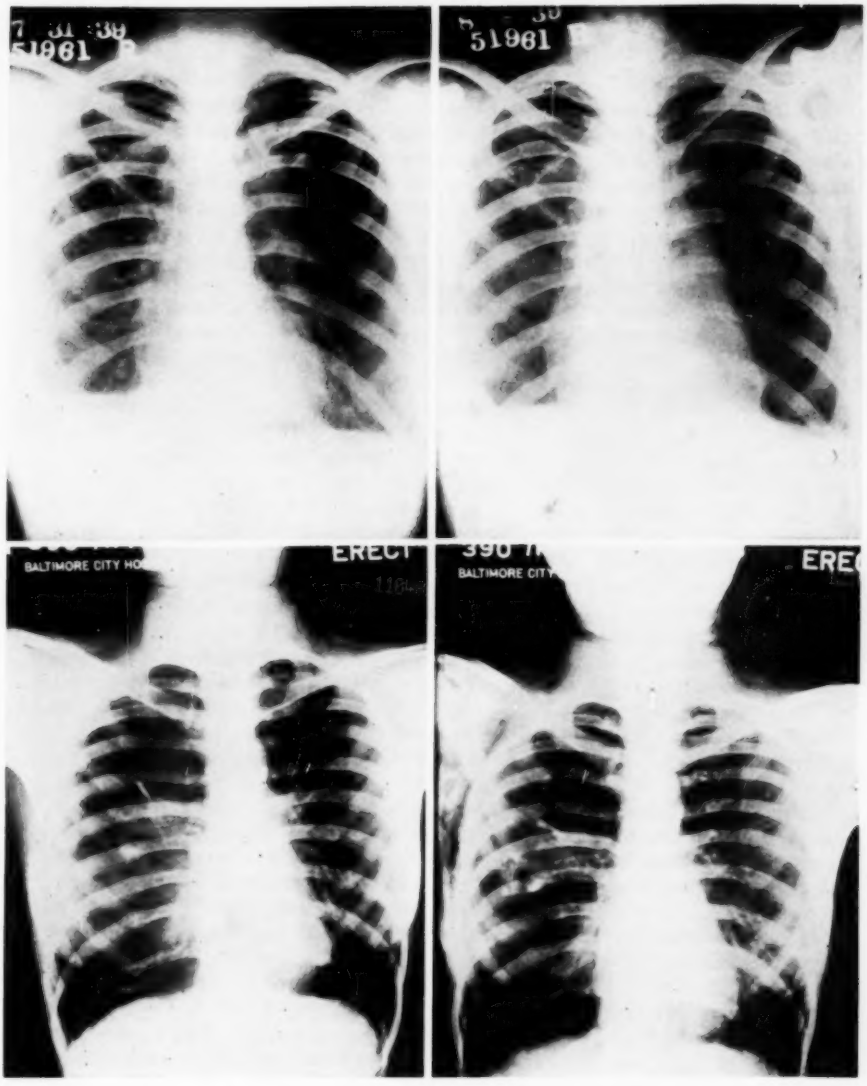

FIG. 7. This series of roentgenograms clearly demonstrates the lungs with reduced intrapulmonic tension (contracting lung) and the lung with increased intrapulmonic tension (tension lung) after closed intrapleural pneumonolysis.

a. (Upper left) The roentgenogram before thoracoscopy was done.

b. (Upper right) A roentgenogram of the same patient about twenty-four hours after complete closed pneumonolysis. There is no subcutaneous emphysema. Because of dyspnea the intrapleural pressure was measured. On inspiration the pressure was found to be −28 cm. of water. As indicated, the lung is atelectatic.

c. (Lower left) The roentgenogram before thoracoscopy was done.

d. (Lower right) The same patient about twenty-four hours after complete pneumonolysis. The subcutaneous emphysema and the tendency of the lung to re-expand can be seen. Subcutaneous emphysema indicates increased intrapleural pressure.

When the operation seems completed the patient is routinely turned successively in the prone, lateral, and supine positions for final inspection of the lung and pleural cavity. Care is exercised not to overlook an adhesion between the two cannulas. The instruments are removed. A silk suture is used to close only the skin at the puncture site. If the lung has been freed completely, 200 to 300 cc. of air are introduced into the pleural cavity and a small dressing is applied. Pressure dressings have not been employed since the cause of subcutaneous emphysema has been understood (17, 18).

The patient is returned to his bed and encouraged to move and turn often and to sit up in bed. This is carried out with great care in order to avoid having the lung lie against the chest wall in one position long enough to become adherent. At operation the lung is judged to have increased, normal, or decreased intrapulmonic pressure (figure 7). A lung with increased intrapulmonic pressure will inflate and cause increased intrapleural pressure, thus forcing the intrapleural air into the tissues through the puncture sites (figures 7c and 7d). If at operation the lung is judged to be of the increased tension type or if there is a question of increased intrapulmonic tension, the patient is given 0.5 cc. of epinephrine 1:500 in oil hypodermically every four hours. Epinephrine is effective as bronchial spasm is the most frequent cause of the increased tension type of lung. Moreover, bronchial spasm may also play a part even though organic bronchial disease may be the exciting cause. Intrapleural operations as well as operations upon the lung frequently initiate temporary bronchial spasm. The patient is examined a few hours after operation and, if the lung type has been judged incorrectly, there may be moderate subcutaneous emphysema, for which epinephrine in oil is given. Most patients have a slight degree of subcutaneous emphysema because moving, coughing, talking, vomiting, defecation, and other actions cause increased intrapulmonic pressure with a corresponding elevation of intrapleural pressures and the escape of air into the tissues through the puncture sites. The state of lung collapse is usually checked by fluoroscopic examination the day after operation. It is unusual for the patient subjected to the closed type of pneumonolysis to require an air injection until several days after operation.

On rare occasions a lung completely freed of adhesions but not markedly collapsed will adhere to the parietal pleura in a few hours. The adherence will be so tight in about twenty-four hours that it cannot be freed by increased refills of air or a change in position. At operation it is difficult to detect the patient whose lung will react in this manner. It seems that in the rare patient even though bleeding is not the cause it is impossible to keep good vision through the eyepiece, since a film forms over the intrapleural lens when it touches any tissue within the pleural cavity. This film cannot be cleared from the lens by brushing it against the lung, as is the usual practice. Such difficulty in keeping the lens clear probably indicates an unusual stickiness of the body fluids and may account for the quick adherence of the lung to the parietal pleura. This is perhaps the opposite of a pleura that reacts by a thin serous exudation. When the sticky type of pleural cavity is found and easy adherence of the lung to the parietal pleura is predicted, steps are taken to avoid the mishap. The lung is collapsed to a greater degree than usual by air injection into the pleural cavity at the completion of operation and the patient is ordered to change position every two hours, day and night, for the first twenty-four hours after operation. Since recognizing the possibility of the sticky type of pleura and lung and adopting the above method of postoperative treatment, in no patient has a lung become adherent to the parietal pleura after pneumonolysis.

Indications for Pneumonolysis

There is only one indication for closed intrapleural pneumonolysis: the patient must be a candidate for artificial pneumothorax, and intrapleural adhesions are

preventing adequate collapse of the lung. It is not within the scope of this paper to discuss the indications for artificial pneumothorax. It is important, however, for the surgeon who performs pneumonolyses to recognize certain contraindications for artificial pneumothorax, which is another way of stating the contraindications for pneumonolysis. It is becoming generally realized that artificial pneumothorax should not be continued if after its initiation one of the following develops: large tension cavity (figure 8 a); an opaque lung (figure 8 b);

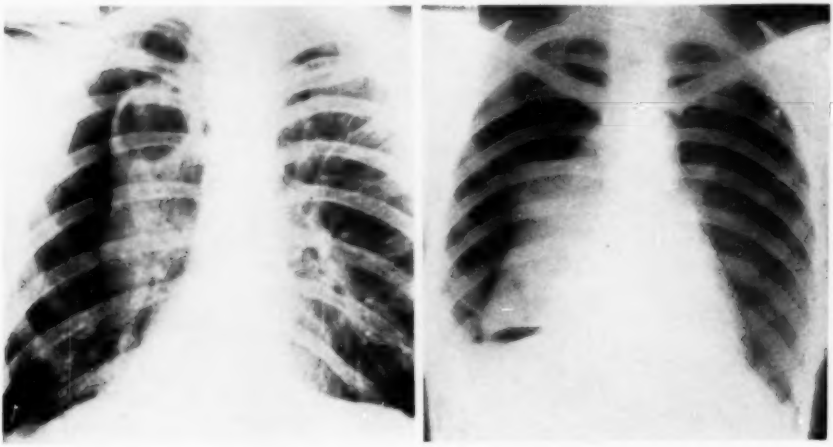

FIG. 8. Two entirely different types of pulmonary tuberculosis are illustrated. In both types of the disease closed intrapleural pneumonolysis as well as pneumothorax are contraindicated.

a. (Left) The roentgenogram reveals a large tension cavity. Under protest of the surgeon the patient was subjected to closed intrapleural pneumonolysis. The lung was freed completely. After bronchoscopic aspiration the cavity appeared to close. The lung became atelectatic, intrapleural fluid developed, which was followed by empyema, a bronchopleural fistula and death. This sequence of events can be expected in patients with disease of this type.

b. (Right) The atelectatic or solid lung, especially with the open cavity, can be expected to follow the clinical course outlined in *a*. Pneumonolysis was refused this patient. Pneumonectomy was accomplished with a successful outcome.

empyema; or the rapid formation of a pleural effusion with or without fever. If the patient is a candidate for artificial pneumothorax and adhesions are found between the lung and the parietal pleura, he should be offered the advantage of closed pneumonolysis. There are no innocent adhesions. A pneumothorax should not be abandoned because of adhesions until a thoracoscopy has been made to determine whether or not the adhesions can be released. Whether adhesions can be released or not cannot be determined by roentgenograms or fluoroscopy (figure 9).

Progress has been slow in developing the routine of early thoracoscopy or pneumonolysis after the initiation of pneumothorax. In 1939 the usual time

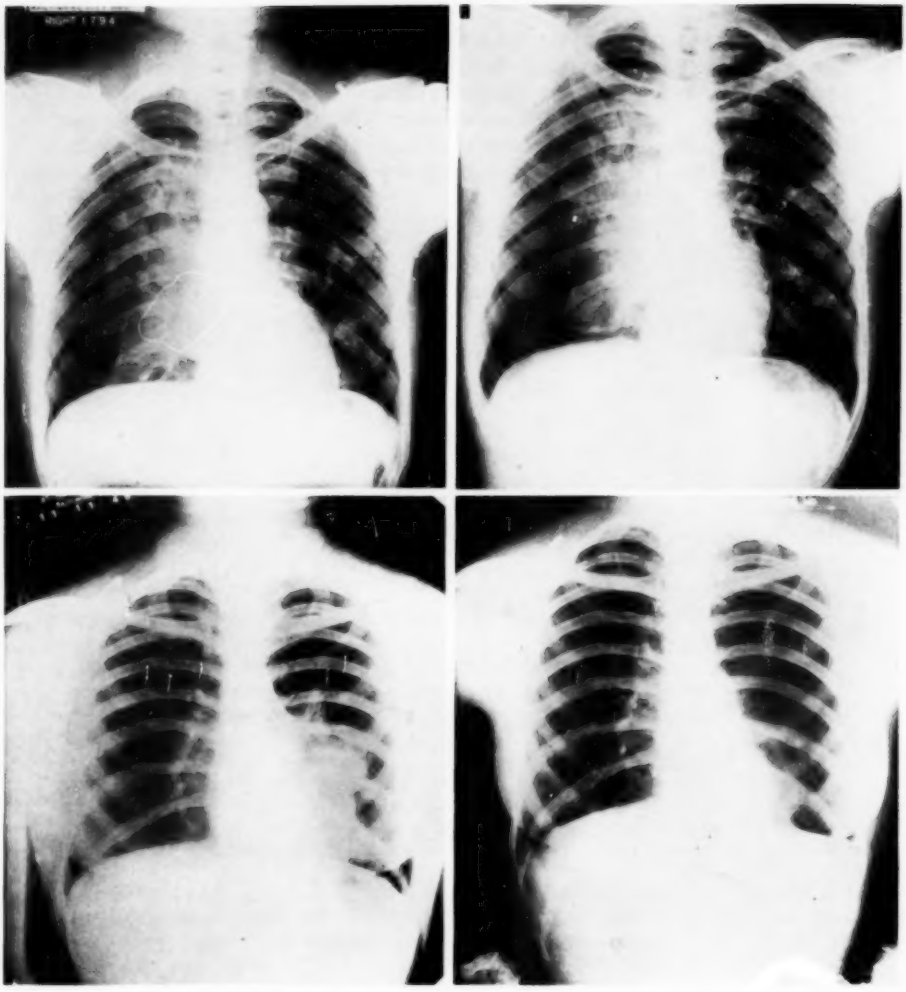

FIG. 9. This series demonstrates the inability to predict by roentgenogram whether or not closed pneumonolysis will be successful.

a. (Upper left) Before thoracoscopy was done.

b. (Upper right) At thoracoscopy it was found that only a few insignificant adhesions could be released. Closed pneumonolysis was thus unsuccessful. The collapse was not changed materially.

c. (Lower left) Before thoracoscopy was done.

d. (Lower right) A complete pneumonolysis was done. The collapse was satisfactory after operation.

interval from the introduction of pneumothorax to closed pneumonolysis was three to six months (1, 19). In patients who have an ineffective collapse of the diseased lung, it seems unwise to permit such a long delay in bringing the disease under control. The time interval has gradually been made shorter. The only requirement at present is that there be enough pneumothorax space in which to manipulate the instruments. Patients have been accepted for pneumonolysis within three days of the initiation of the pneumothorax. It was feared in the beginning that re-expansion or the loss of pneumothorax space would occur more frequently, but it does not. It is evident that more patients can have their lung freed completely from the parietal and mediastinal pleura if the pneumonolysis is done within two weeks of the initiation of pneumothorax. In that period, adhesions and endothoracic fascia do not have a chance to thicken or undergo fibrosis. When early pneumonolysis is accepted and practiced, a patient can have a pneumothorax induced, a closed or open type of pneumonolysis, and the diseased lung under control in two to three weeks. In addition to the great advantage to the operator, the time saved the patient would justify the adoption of early pneumonolysis.

RESULTS

The present series concerns 608 patients operated upon between October, 1938 and December, 1946, or an eight year period. The follow-up period on these patients extends to December, 1947. The patients have been obtained from all the sanatoriums in Maryland, both privately owned and state and city controlled, as well as from doctors in the private practice of medicine in Maryland.

The report is marred by the inability to make the study complete. It has been impossible to find the charts of 97 patients. Unfortunately, many of the lost charts overlap the 109 patients reported in 1941 (20). The charts are missing for a few patients operated upon in 1938. The source of the patients and the place of operation have been highly diversified. The method of record keeping and changes in systems of filing have accounted for the high percentage of missing charts. The analysis of operative data thus concerns 511 patients. Certain facts now desired were not recorded in the notes of operation during the early years. Therefore, in 45 cases it is unknown whether the operation was thoracoscopy only or pneumonolysis, complete or incomplete. For the same reason the condition of the pleura at the time of operation is not known in all patients.

It seems logical that the patients be divided into Negroes and whites and that the patients from sanatoriums privately owned and from doctors in private practice be separated from those patients from sanatoriums under state or city control. All the patients have been operated upon by the writer. All but 3 were operated upon under local anesthesia. In tables 1, 2 and 3 the results are given as briefly as possible. In table 1 the years of follow-up are indicated since they extend to December, 1947. There were 301 females and 210 males. The youngest patient was five years of age and there were 137 patients twenty years of age or younger. The oldest patient was fifty-eight years of age and only 9

TABLE 1
Composition of series

SOURCE OF PATIENTS	YEAR OF OPERATION	NUMBER OF PATIENTS	OPERATION			LIVING AND WELL PNEUMOTHORAX MAINTAINED		LIVING AND SICK PNEUMOTHORAX MAINTAINED		CONDITION UNKNOWN	DEAD
			Pneumonolysis		Thoracoscopy only						
			Complete	Incomplete		Yes	No	Yes	No		
Private doctors and sanatoriums	1939 through 1941	20	11	6	3	3 1 1	3 1 1	2 0 1	2 1 0	1 3 0	0 0 0
	1942 through 1944	94	48	33	13	19 5 2	20 11 4	1 3 1	2 2 0	5 4 2	1 8 4
	1945 through 1946	56	23	21	12	13 8 2	3 3 3	2 3 1	0 2 2	3 5 4	2 0 0
State and City Sanatoriums	1939 through 1941	60	33	17	10	2 1 0	2 6 4	1 0 0	0 1 0	26 4 5	2 5 1
	1942 through 1944	76	37	27	12	10 3 0	12 6 2	1 1 0	1 5 2	7 6 6	6 6 2
	1945 through 1946	27	14	8	5	6 4 2	1 1 1	0 0 0	1 0 1	6 3 1	0 0 0
Negro	1939 through 1941	125	60	41	24	1 0 1	14 9 3	0 1 0	3 1 1	7 6 2	35 24 17
	1942 through 1944	8	5	1	2	0 0 0	0 0 0	0 0 0	0 0 1	3 0 1	2 1 0
	1945 through 1946	0									

were fifty years old or older. The present status of 104 patients is unknown. One hundred thirty-six of the patients are dead (table 2). Of this group 131 died of tuberculosis in some form and 5 died of causes not related to tuberculosis. There are living and sick 45 patients and 29 of these are ill because of disease in the contralateral lung. One hundred ninety-eight patients are living and well. In the living and well group 84 patients still have a pneumothorax and 114 do not

TABLE 2

Late complications and cause of death

OPERATION	NUMBER	EMPYEMA						BRONCHO-PLEURAL FISTULA		OBLITERATIVE PLEURITIS		COMPLICATIONS NOT PLEURAL		DEATH	
		Tuberculous		Mixed		Pyogenic								Tuberculosis	Other
		L	D	L	D	L	D	L	D	L	D	L	D		
Complete	231	2	7			1	1			1		4	7	44	4
Incomplete	150	8	5		1			1	1	2		8	7	43	1
Thoracoscopy	85	4	1		1			2	1			1	7	24	
Unknown type	45				1							3	1	20	
Total	511	14	13		3	1	1	3	2	3		16	22	131	5

TABLE 3

Time from initiation of pneumothorax to closed pneumonolysis

DAYS	NUMBER OF PATIENTS	THORACOSCOPY ONLY	COMPLETE PNEUMONOLYSIS	INCOMPLETE PNEUMONOLYSIS	UNKNOWN
0 to 5	8	2	3	3	0
6 to 10	34	1	16	17	0
11 to 20	55	6	29	20	0
21 to 40	53	8	15	17	13
41 to 60	82	4	33	17	28
60 plus	155	34	82	39	0
Unknown	124	30	53	37	4
Total	511	85	231	150	45

have a pneumothorax. Of the 114 all have had their disease arrested by pneumothorax, except 6 patients who underwent major surgery in order to arrest their disease. In this group the supplemental phrenic operations have not been tabulated. Approximately two-thirds of the pneumothoraces in the entire group, including those now well and sick were abandoned as an elective procedure. Two pneumonolyses were done on 61 patients and the second operation resulted in complete pneumonolysis in 21 of the patients. Three pneumonolyses were done on 8 patients and complete pneumonolyses were accomplished at the third operation on 3 of the patients. The early complications were rather few. Hemorrhage of mild degree occurred in 28 patients. It is estimated that in the most

severe hemorrhage not more than 100 cc. of blood were lost. In the majority only a few cubic centimeters of blood were lost. One patient had a spontaneous leak of air from the lung about twelve hours after operation. The lung was made to completely re-expand by catheter suction. The loss of pneumothorax space was the only ill effect, even though the patient had a bilateral pneumothorax at the time of the accident. The pneumothorax space was lost in 3 other patients. One patient died three days after thoracoscopy without pneumonolysis. The cause of death was never accurately determined. One patient developed pyogenic empyema and subsequently lost her life. In 6 patients the lung was reattached to the parietal pleura in the first twenty-four hours after complete pneumonolysis. Persistent pleural fluid (not empyema) was found in 28 patients. Tuberculous empyema (Table 2) occurred in 27 patients and 13 of these died. Where the pleura was delicate and normal at the time of operation, tuberculous empyema occurred in 1.6 per cent of the cases. Where the pleura was abnormal, that is, inflamed or presented tubercles, fibrin or fluid, the incidence of tuberculous empyema was 7 per cent. Spontaneous pneumothorax occurred in 6 patients. Five of these developed bronchopleural fistulas, whereas one suffered no ill effects. Of the 5 with bronchopleural fistulas, 3 developed mixed infection empyema but are alive and the other 2 patients are dead. The development of bronchopleural fistulas with mixed infection empyema or death occurred long after operation and may have been unrelated to operation. A pleurocutaneous fistula was found in one patient. Obliterative pleuritis occurred in 3 patients, with a late loss of pneumothorax space. Other complications did not involve the pleura and included such conditions as hemoptysis and tuberculous meningitis.

It would appear that whether or not the patient is cured of pulmonary tuberculosis depends upon the effectiveness of pneumothorax as a method of treatment and therefore late therapeutic results might not be considered relevant in a discussion of the closed type of pneumonolysis. There are many factors closely associated with this closed operation, however, that will affect the end result. The various early and late complications and whether the lung was partially or completely freed are factors directly associated with the operation. The patient who is not a candidate for artificial pneumothorax should not have a pneumonolysis. Moreover, it is possible to have successful pneumonolysis and artificial pneumothorax on one side and yet have the patient die from disease in the other lung. Furthermore, disease in the other lung might necessitate the abandonment of an effective pneumothorax following pneumonolysis. An effective pneumothorax after pneumonolysis could be handled badly and produce a poor result. In spite of all these factors it seems proper that the closed intrapleural pneumonolysis be held chiefly responsible for the final results obtained. It would be extremely interesting to compare a group of patients who have effective pneumothorax without pneumonolysis with a group of patients subjected to pneumonolysis which rendered the pneumothorax effective.

It is obvious that there is no satisfactory classification for tuberculosis and, therefore, there is no adequate means for comparing groups of patients. The

Negro group of patients show an overall death rate of 67.5 per cent as compared to the 15.1 per cent (table 1) for white patients. However, the group of white patients under the care of private doctors and private sanatoriums had an overall death rate of 10.5 per cent compared to 22.2 per cent (table 1) for the state and city sanatoriums group. It is perhaps impossible to correlate these series-mortality figures with the observations of other investigators. It may be desirable, however, to present the mortality rate for pulmonary tuberculosis in the state of Maryland. The fate of all patients discharged from the state sanatoriums was followed for five years beginning in 1934 (21). After five years the mortality rate in the white patients was as follows: far advanced disease, 62 per cent; moderately advanced disease, 25 per cent; and minimal disease, 6 per cent. In the Negro group the mortality rate after five years was as follows: far advanced disease, 78 per cent; moderately advanced disease, 40 per cent; and minimal disease, 19 per cent.

In the present series the recovery rate for the Negro is 24 per cent as compared to 69 per cent (table 1) for the white patient. When the two white patient groups are compared there is found recovery in 72.7 per cent of the private patients as compared to 63.6 per cent for the state and city patients. As would be expected, the follow-up on the private patient group is better than in the other group of white patients, that is, 84.2 per cent as compared to 60.8 per cent. The follow-up is exceptionally good on the Negro patients, 82 per cent (table 1). Many of the Negro patients are still ill or are dead and the number of fatalities can be ascertained through the Bureau of Vital Statistics.

The question arises as to whether the difference between the death rate in white and Negro patients is attributable to the difference in the economic status of the two groups. When the two groups of white patients are compared, it can be seen that the economic factor is important for here there is no important racial difference to be considered.

In the early years of the study the indications for pneumothorax were not understood as well as at present. Undoubtedly, many patients were subjected to the closed type of pneumonolysis when they were not satisfactory candidates for the procedure. Thus, late complications were probably higher and the death rate from tuberculosis greater than would be the case under present standards and indications. Several of the patients developed bronchopleural fistulas because of large tension cavities and opaque lungs. At present pneumothorax would not be continued in such patients and they would probably be subjected to pulmonary resection rather than be accepted for the closed form of pneumonolysis.

If pneumonolysis is considered a procedure to be judged by early complications and whether or not the operation is successfully accomplished, the record would indicate that it is a safe operation. The series-mortality rate is 2 patients of the 608 who were subjected to 685 operations. The lung was completely freed of adhesions in 49.5 per cent of the patients and was incompletely freed in 32.1 per cent of the patients. Thoracoscopy followed by inspection only was performed in 18.2 per cent of the patients. The pneumothorax space was lost in 4 of the patients. A record of such low mortality and morbidity would indicate that

all patients with adhesions should be subjected to the closed type of pneumonolysis provided that the patient was originally a suitable candidate for pneumothorax. The belief is strengthened when it is realized that the incidence of late complications are certainly no greater after the closed form of pneumonolysis than without the operation. The incidence of tuberculous and mixed infection empyema was 3.8 per cent when the lung was freed, 9.3 per cent if the lung was freed incompletely, and 7 per cent when adhesions were not disturbed. The incidence of empyema occurring in pneumothorax without pneumonolysis as found by Eglee and Wylie (22) was 7.8 per cent. These writers also summarized the reports of six others who gave the incidence of tuberculous and mixed infection empyema as ranging from 5.8 to 14.4 per cent. Alexander (1), however, reported the incidence as ranging from none in 600 cases to 21 per cent in 151 patients having pneumothorax without pneumonolysis. Even though the mortality rate is higher in the Negro patient, the incidence of complications including empyema is essentially the same as in the white patient.

By definition a complete pneumonolysis is accomplished when the lung is freed completely of all adhesions. A patient with complete pneumonolysis should have the best prognosis for healing of the lung disease. In the private patient group 84.6 per cent (table 1) of these patients are living and well. In the state and city sanatorium group of patients there are 73.3 per cent living and well after complete pneumonolysis. The results of complete pneumonolysis should be compared with results when thoracoscopy only was done. In both white patient groups approximately 60 per cent are living and well. It is not satisfactory to consider the incomplete pneumonolysis group for judgment must be exercised as to whether the resulting collapse will be adequate or inadequate. Many will be no better after incomplete pneumonolysis than after thoracoscopy.

The percentage of patients who were subjected to thoracoscopy without pneumonolysis seems rather high (18.2 per cent). It should be noted, however, that patients were not selected for operation from the standpoint of whether or not the adhesions could be released. If pneumothorax was initiated and the collapse was inadequate because of adhesions, the operation was undertaken even though freeing of the lung seemed impossible by roentgenogram or by fluoroscopy. Thoracoscopy is of definite help to the patient because at times it provides information leading to the early abandonment of an unsatisfactory pneumothorax.

Patients whose lung did not collapse well under proper refill treatments were subjected to operation whether or not adhesions could be demonstrated. Fifteen such cases were encountered and 3 of these patients did not have adhesions. They are included in the group with thoracoscopy without pneumonolysis.

It would seem that the early closed type of pneumonolysis after the initiation of pneumothorax was not carried out consistently (table 3). It was difficult to make known the advantages of early pneumonolysis. There is also the difficulty of promptly obtaining a bed in the general hospital. Occasionally there is a distinct advantage in withholding pneumonolysis for several weeks for adhesions sometimes stretch out. These cases are in the minority. It is true that in some patients the adhesions stretch considerably under careful pneumothorax treat-

ment. It should be pointed out that the force used to stretch an adhesion is made possible by the pneumothorax. However, the intrapleural pressure used is only a small factor in the stretching of most adhesions. The weight of the lung falling by gravity exerted upon the adhesion is the most important factor in the stretching of the adhesion. If the position of the adhesions were known, the patient undoubtedly could be urged to assume the position that will allow the weight of the lung to fall upon the adhesion. This maneuver has been used in the patients who have had incomplete pneumonolyses and occasionally it has proved successful as the lung could be freed completely at subsequent operations. It would appear that this factor could be used in patients who have not yet been subjected to operation. The posteriorly placed adhesions are the ones which most frequently defy release by operation. It is true that most tuberculous disease is posterior in the lung but it is likewise true that most patients, whether they have pneumothorax or not assume the supine position more often than any other position and particularly more frequently than the prone position.

Hemorrhage of varying degrees occurs in every patient subjected to the closed type of pneumonolysis. Some blood must escape from the trocar site into the pleural cavity. Whenever it was necessary to cauterize a blood vessel to stop oozing or brisk bleeding, the case was tabulated under hemorrhage and 28 cases occurred in the series. In no instance did a hemorrhage of more than an estimated 100 cc. occur, nor was a transfusion of blood or plasma ever necessary.

Obliterative pleuritis is thought to develop frequently after free blood has been found in the pleural cavity (23). In the series of 28 patients tabulated as having had hemorrhage at the time of operation, not one developed obliterative pleuritis. In the entire series, obliterative pleuritis occurred in only 3 patients and all the patients operated upon had some blood escape into the pleural cavity.

SUMMARY

1. The open type of pneumonolysis may be indicated when the closed method fails to accomplish a satisfactory collapse of the lung. The open form is a good method of treatment in selected patients.

2. The individual operator is more important than the choice of a one or two piece pneumonolysis instrument or the selection of galvanocautery or electrosurgery as the cutting method.

3. When possible, adhesions should be released and not divided.

4. The indication for closed pneumonolysis is the presence of intrapleural adhesions in a patient who is a candidate for artificial pneumonothorax.

5. Closed pneumonolysis usually is accomplished advantageously in a few days after initiation of the artificial pneumothorax.

6. The closed type of intrapleural pneumonolysis is a safe operation, but its value should not be dissociated from the end results of pneumothorax treatment.

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THE DIAGNOSTIC PROBLEM OF PRIMARY PLEURAL EFFUSIONS[1]

JOSEPH R. KRAFT

INTRODUCTION

The accepted practice at present is to consider all primary pleural effusions as tuberculous or "probably tuberculous" until proved otherwise. It is well recognized that substantial differences in regard to prognosis and treatment exist between tuberculous pleural effusions and the benign effusions of other etiology. Unfortunately, there are available no generally applicable diagnostic methods for the ready identification of the various forms of primary pleurisy. In the absence of diagnostic tests, it was believed that it might be worth while to review a large series of cases of primary pleural effusion with particular attention to the diagnostic problems involved. Such a review constitutes the basis for the present report.

OBSERVATIONS

Composition of Series

One hundred patients with serous pleural effusion observed on the tuberculosis service of Fitzsimons General Hospital, Denver, Colorado, have been reviewed. The patients were admitted to this hospital within a period from May, 1947 through January, 1948. No pleural effusion which appeared in association with, or subsequent to, known pulmonary disease or a surgical procedure was included in this series. Therefore, the cases reviewed may be considered "primary." Only those cases in which observations were made for a minimum of six months in the hospital are included.

Classification

The cases were grouped according to roentgenographic evidence of parenchymal disease and the results of studies of sputum and pleural fluid after a minimum of six months or more of hospitalization. Group I consisted of 55 cases without evidence of pulmonary lesions or abnormal laboratory findings. Group II consisted of 24 cases without evidence of pulmonary disease but with bacteriologic evidence of tuberculosis. Group III consisted of 21 cases in which evidence of pulmonary disease (with or without positive bacteriologic tests) was detected after the appearance of the effusion.

The series is necessarily a select group as it consists only of American males (97 soldiers and 3 veterans). Sixty-two per cent were in the age group 18 to 21 years and 90 per cent were in the 18 to 30 year old group. The youngest patient was 17 and the eldest, 39 years of age. The series of 100 cases included Negroes and 7 Japanese-Americans (table 1). The great majority of the cases (97 per cent) were transferred from other Army hospitals. Seventy-one per cent of the patients developed their illness while on foreign duty (table 2).

[1] From the Medical Service, Fitzsimons General Hospital, Denver, Colorado.

None of the patients recalled having been exposed to tuberculosis during civil life. Of those with foreign service, only 6 had definite tuberculosis exposure while an additional 9 had had questionable exposure. With the known high prevalence of pulmonary tuberculosis in Germany and the Far East, it may be assumed that these patients were exposed to the disease.

Of the 100 patients in the series, 46 had right-sided effusions and 54 had left-sided effusions. There were only three instances of bilateral effusion. Mantoux

TABLE 1

Racial composition of series

	GROUPS		
	I	II	III
White	45	21	13
Negro	8	1	5
Japanese-American	2	2	3
	—	—	—
	55	24	21

Total: 100 cases.

TABLE 2

Incidence of foreign service

	GROUPS		
	I	II	III
Germany	20	8	2
Japan	21	5	3
Korea	6	3	0
Others*	1	1	1
	—	—	—
	48	17	6

Total: 71 cases.

* Guam, Laborador, Puerto Rico

and coccidioidin (1:1,000) skin tests were performed on all cases. Seventy-seven reacted positively to the first strength PPD and 23 were positive to second strength. Eight patients reacted positively to coccidioidin (one plus). The pleural fluids of 3 of these patients were positive for tubercle bacilli on guinea pig inoculation. The remainder had never been in any of the areas where coccidioidomycosis is known to be endemic. The coccidioidin skin tests were evaluated as insignificant.

Symptoms

As may be seen in table 3, chest pain, varying from a dull to a sharp, piercing pain, more marked on deep respiration, was the predominant complaint (94 per cent) and was usually associated with fever and malaise (88 per cent). The pain

and the effusion always occurred on the same side of the chest. The associated fever would usually vary from 99 to 103° F. Only one patient had a fever as high as 105° F. He was considered to have an atypical pneumonia with effusion until the presence of tubercle bacilli in the pleural fluid was demonstrated. In the entire series the average duration of fever was eighteen to twenty-one days. A duration of four to six weeks was not uncommon. The fever usually terminated by lysis and did not appear to have been affected by chemotherapy. Seventy-two patients received penicillin, 25 were given sulfonamide alone or in conjunction with penicillin, and 3 were treated with streptomycin.

It was noted that in 15 patients with a fever of 103° F. or higher a gradual drop to a low grade fever followed aspiration of the pleural fluid. Conversely, the low grade fevers seemed relatively unaffected by aspiration of the fluid.

Eighty-two of the 100 patients lost weight during their illness. The amount of loss varied from 5 to 20 pounds. The loss of weight occurred principally during the acute or febrile phase of the illness. This weight was usually regained quite readily following termination of the acute phase.

TABLE 3

Subjective symptoms

TOTAL		GROUPS		
		I	II	III
94	Chest pain	53	22	19
88	Malaise and fever	48	20	20
25	Cough and sputum	14	6	5
12	Dyspnea	6	4	2
82	Weight loss	40	22	20

It was particularly interesting to note the relatively insidious onset of symptoms in primary pleural effusions. A careful history of subjective symptoms, with particular emphasis on onset of chest pain, revealed that 73 per cent experienced the onset of symptoms one or more weeks prior to hospitalization. The initial onset was usually one of intermittent, transitory chest pain, occasionally "sharp", but usually dull. Increased chest pain plus fever and malaise would usually force the patient to seek medical aid. The duration of symptoms before seeking medical care was two to seven days in 27 per cent of the group; eight to fourteen days in 30 per cent; fifteen to twenty-one days in 20 per cent; and twenty-two to twenty-eight days in 15 per cent (table 4). Four patients had had symptoms for three months prior to hospitalization and one patient had been ill for five months. It was also noted that in 10 patients the pleural effusions were discovered by routine chest roentgenograms. In three of these no history of any symptoms could be elicited.

Of the 100 cases reviewed, in only 10 were the initial subjective symptoms of chest pain sufficiently severe to warrant seeking prompt medical aid. Roentgenographic examinations at the time of onset of the pain were negative. Sub-

sequent roentgenographic examinations, following recurrence or aggravation of symptoms, revealed the presence of an effusion. Four of these cases were in group I and three were in groups II and III, respectively.

In only 11 instances was it possible to note the relative progression of effusion. Three of these patients developed effusion during hospitalization for other causes. Symptoms had been present for two to four days before the first roentgenographic examinations. These revealed haziness of the lateral lower lung field at the level of the sixth or seventh anterior rib with blunting of the costophrenic sulcus or with definite evidence of fluid. Serial roentgenographic and fluoroscopic examinations revealed that the maximum amount of fluid was demonstrated in these cases between the fourteenth and the twenty-first days after the onset of symptoms. Of these 11 cases, 5 were in group I, 4 in group II, and 2 in group III.

TABLE 4

Duration of symptoms prior to hospitalization

PER CENT	TIME	GROUPS		
		I	II	III
27	2 to 7 days	17	6	4
30	8 to 14 days	14	10	6
20	15 to 21 days	11	5	4
15	22 to 28 days	8	2	5
5	one month, plus	3	0	2
3	no symptoms	2	1	0
100	Total.....	55	24	21

With the triad of chest pain, fever and malaise, and the roentgenographic findings of haziness in the lateral lower lung field, a preliminary diagnosis of atypical pneumonia with effusion was made in 7 of the 11 cases.

Laboratory Data

In the 90 cases which were aspirated, the fluid was generally described as clear amber (91 per cent) or cloudy amber (9 per cent). There were no instances of purulent or bloody fluid in this series. The specific gravity of the fluid was typical of exudation (1), *i.e.*, usually above 1.015 and invariably above 1.012.

Of the effusions aspirated, 51 were tested by guinea pig inoculation with 18 positive results (35 per cent); 30 effusions were tested by culture alone of which 2 were positive for tubercle bacilli. It should be noted that of those tested by guinea pig inoculations 24 were, in addition, tested by culture. Nine fluids were positive for tubercle bacilli with both tests. Cultures of 80 fluids for microorganisms other than *M. tuberculosis* were uniformly inactive. It should be noted that the animal inoculations and cultures reported above were single tests. Repetition of these examinations would have been highly desirable.

Regardless of method, the erythrocyte sedimentation rate was markedly elevated at the onset of the effusion. The elevation would persist long after the

acute febrile phase of the illness had subsided. In many cases the elevation persisted the entire period of observation (six to eight months) prior to transfer of the patient to a Veterans Hospital. It was noted that the course of the sedimentation rate seemed directly related to the regression of the pleural fluid or fibrinous pleurisy. All patients with a minimal fibrinous pleurisy which was stable roentgenographically for two or more months within six months of onset had sedimentation rates within normal limits. This was also true of 5 patients who subsequently developed parenchymal lesions (table 6, cases 7, 9, 16, 17, 18).

Sixty-two per cent of the patients had total leucocyte counts which were within normal limits (2). In every instance the differential counts were within the normal range, including the determinations in the 28 patients with a mild

TABLE 5

Laboratory examinations of pleural fluid and sputum

	GROUPS		
	I	II	III
*Specific gravity above 1.015	41	20	14
*Specific gravity below 1.015	2	1	2
Lymphocytes predominate	42	19	14
Polymorphs predominate	1	2	2
Positive guinea pig inoculation for *M. tuberculosis*	0	15	3
Positive culture *M. tuberculosis*	0	2	0
*No aspiration	7	1	2
*Results unknown	5	2	3
Sputum positive for *M. tuberculosis*	0	8	8
	55	24	21

* Total—100

leucocytosis (up to 12,500 per cm^3). The erythrocyte and hemoglobin determinations were all within normal limits.

Occurrence of Parenchymal Disease

In this series of 100 cases, 21 subsequently developed roentgenographically demonstrable parenchymal disease following the onset of the pleural effusion (table 6). It should be emphasized that no instance of effusion concomitant with known parenchymal disease or primary complex was included in the series. In all but 3 cases roentgenograms obtained two to twenty-four months before the onset of effusion were available. In the 3 without previous films, it was possible to observe the parenchymal lesions roentgenographically following the onset of effusion.

All of the parenchymal lesions were minimal in extent except two (cases 6 and 7) which were moderately advanced. The apical lesions were typical of reinfection pulmonary tuberculosis. Ten lesions were suggestive of a primary parenchymal focus. In only 2 of these cases (7 and 19) was an associated hilar

adenopathy typical of a primary complex noted. In all of the patients except cases 7, 13, and 17, detailed below, the parenchymal lesions were demonstrated roentgenographically during a regimen of bed-rest.

TABLE 6

The occurrence of parenchymal disease (Group III)

CASE NUMBER	LAST NORMAL ROENTGENOGRAM	CHRONIC FIBRINOUS PLEURISY AT SIX MONTHS (OR AS INDICATED)	ROENTGENOGRAPHIC ONSET OF LESION IN MONTH AFTER ONSET OF FLUID	FLUID FOR *M. tuberculosis*	SPUTUM EXAMINATION FOR *M. tuberculosis*; MONTH FOUND	SITE OF LESION
	months					
*(1)	2	m[3]	2	negative	+ (8)	Apex (right)
(2)	6	M	10	+	negative	RLL
(3)	3	M	9	negative	+ (6)	RLL
(4)	12	M	3	—	negative	Apex (right)
(5)	18	m[5]	4	—	negative	Apex (right)
(6)	—	M	6	negative	+ (5)	Apex (right)
(7)	12	m[2]	6	negative	negative	RUL
(8)	18	M	8	negative	negative	LLL
(9)	6	m	6	—	negative	LLL
(10)	23	M	6	—	+ (8)	LLL
(11)	15	M	5	negative	negative	LUL
(12)	18	m	6	negative	negative	Apex (right)
(13)	—	M	10	negative	negative	RUL
*(14)JA	8	m	6	negative	+ (5)	RLL
(15)JA	10	M	3,6	negative	+ (5)	Apex (bilateral)
(16)JA	2	m	6,8	negative	negative	Apex (bilateral)
(17)N	22	m	8	negative	+ (9)	Apex (left)
(18)N	9	m	6	negative	+ (8)	Apex (right)
(19)N	12	M	6	negative	+ (6)	RLL
(20)N	24	M	7,9	+	+ (9)	Apex (bilateral)
*(21)N	—	m[4]	3	+	negative	Apex (bilateral)

M: moderate chronic pleurisy extending laterally up to the fourth anterior rib
m: minimal chronic pleurisy extending laterally up to the sixth anterior rib or less
JA: Japanese-American
—: results unavailable
N: Negro
*(): bilateral effusion

Case 7: The patient had been hospitalized three months for atypical pneumonia with effusion. The fluid negative for tubercle bacilli and a chronic minimal pleurisy persisted. Three months later, at the separation center, a minimal parenchymal focus with associated hilar adenopathy was visible on a roentgenogram of the chest. Regression of the lesion was noted after four months of bed-rest.

Case 13: After six months hospitalization for primary pleural effusion, the patient went A.W.O.L. for six weeks. Upon return, a minimal parenchymal focus was demonstrable on the chest roentgenogram.

Case 17: The patient was hospitalized for primary pleural effusion. The fluid, which was negative for tubercle bacilli, disappeared almost completely after six months' hospitalization. No parenchymal lesion was noted at this time but after the return of the patient from

a convalescent furlough (forty-five days) a minimal apical lesion was discovered. Tubercle bacilli were present in the sputum. The lesion progressed to cavitation.

Three patients had bilateral effusions with initial onset on the right and subsequent contralateral effusion at two and one-half, three, and four months, respectively. One of the patients (case 21) developed bilateral, minimal apical lesions three months after the onset of the pleurisy, a peritoneal effusion six months later, and tuberculous meningitis confirmed by culture eight months after the onset of the pleural effusion. This was the only case comparable to those reported by Fernandes (2) who believes that bilateral pleural effusion is frequently a manifestation of miliary tuberculosis.

The results of the bacteriologic examinations of the sputum are presented in table 6. It is granted that the finding of a parenchymal lesion did prompt repeated and intensified studies of the sputum. Bronchoscopy of all patients whose sputum contained *M. tuberculosis* revealed no endobronchial disease. All of the parenchymal lesions were initially noted upon the same side as the effusion, including 3 of the instances of bilateral effusions. In the remaining instance (case 21) with bilateral lesions, it was impossible to determine which lesion developed first, for both were noted upon the same roentgenographic examination.

Pathogenesis

Israel and Long (3) have reported that primary tuberculous infection in adults, as evidenced by a change in tuberculin sensitivity from negative to positive, may be followed after a short interval by an attack of pleurisy.

Erwin (4) in 1944 postulated reasons why an intrathoracic primary complex might be expected to produce direct infection of a highly allergic pleura with tubercle bacilli penetrating either from a subpleural parenchymal focus, or from a caseous tracheobronchial lymph node.

Thompson (5) accepts this theory and refutes the theory of post-primary dissemination by the blood stream on the basis of his observations on 190 cases.

The Erwin theory, especially as elaborated by Thompson, may quite well be the explanation of pathogenesis of many of the cases in the present series. As previously noted, all of the patients had positive tuberculin skin tests. A good deal of information favoring or refuting Erwin's theory could have been obtained from the present series had the history of tuberculin conversion been known.

Prognosis

It is granted that the time period of observation of the cases reviewed is short and that much must be speculated in regard to the eventual course of the cases. It should be noted that a long term survey of primary pleural effusion cases (including cases reviewed) is currently being evaluated by Dr. Wm. H. Roper, Director of Minimal Tuberculosis Research, Fitzsimons General Hospital (6). However, it is significant to note that 21 per cent of the present series developed pulmonary tuberculosis within one year (average 6.2 months) after the onset of pleural effusion. In regard to prognosis, this percentage may be compared with

Thompson's (7) findings where 12 per cent of 190 patients with pleural effusion developed a parenchymal lesion within the first year and a total of 25 per cent within five years.

Bonilla's (8) report may also be applied with some concern to the cases reviewed, for in his group of 40 patients with pleural effusions without any pulmonary infiltration, the parenchymal lesions developed in the whites in an average of 38 months, and in the Negros 21.3 months after the pleurisy.

Jones and Dooley (9) demonstrated that pleural effusion may be a manifestation of extrapulmonary tuberculosis, especially in the Negro. They also emphasized the necessity for a guarded prognosis in Negro patients with effusion, for in their series of 99 cases followed for more than one year 15 per cent eventually died of tuberculosis which was principally of an extrapulmonary form. In the total cases reviewed in the present report, only one presented evidence of extrapulmonary tuberculosis during the short time of observation. It was an instance of renal tuberculosis in a Negro of group I.

COMMENT

Although it is generally accepted that a primary pleural effusion is frequently a manifestation of tuberculosis, the insidious onset, chest pain, fever and malaise do at times present problems of differential diagnosis.

In this series of 100 cases, 24 were originally considered to have nontuberculous diseases, including pneumonia with effusion, bronchitis, and malaria. The diagnosis of atypical pneumonia with effusion was most common. This error occurred especially when the patient presented himself after a relatively short duration of symptoms and only a minimal effusion was demonstrable roentgenographically at the onset of the illness. Particular reference is made to the cases of atypical pneumonia with effusion as cited by Turner (10). Several of his examples were comparable with almost any one of the 27 patients of the present series who had had symptoms for less than one week. Of the 24 cases that were originally considered to have diseases other than tuberculosis of the pleura, 13 were in group I, 7 in group II, and 4 in group III.

Examination of the fluid may give much information in regard to etiology and at times may establish the diagnosis (11 to 17). The importance of a positive finding of tubercle bacilli on culture or guinea pig inoculation of the pleural fluid is evident. Nevertheless, the relatively low incidence of successful isolations of tubercle bacilli from the pleural fluids of the present series (35 per cent) and in other reports (5, 18, 19) serves to emphasize that the diagnosis for the most part depends upon careful differential diagnosis and clinical experience.

Since many of the effusions were tested at other hospitals, the techniques employed are unknown. At the laboratories of Fitzsimons General Hospital, according to Fisher (20), the centrifuging of large amounts of pleural fluid followed by guinea pig inoculation of the resulting sediment produces the most favorable results. Granting that with a uniformly optimal technique, the results might have been somewhat better, the problem is not appreciably lessened.

The necessity, because of the lack of absolute certainty, to designate those in-

fections in which the etiology has not been demonstrable, *e.g.* group I, as "probably tuberculous" occurs. The possibility that these cases may represent other diseases, *e.g.*, atypical pneumonia or rickettsial infections, cannot be completely excluded.

As noted in the cases reviewed, it is impossible to foretell which infections may progress to the development of parenchymal or other lesions. Hence, in the light of current knowledge, treatment must be initiated empirically.

The treatment of primary pleural effusion had dual objectives. The maximum removal of fluid in an effort to limit the chronic fibrinous and eventually fibrous pleurisy to a minimum may be cited as one objective. The other is bed-rest for the underlying tuberculous lesion, whether it be visible or invisible on roentgenographic examination. This bed-rest may be considered as prophylaxis rather than therapy. It is recalled that, in the majority of the 21 cases with lesions, the latter appeared while the patients were on bed-rest. Three cases were also cited that demonstrated the dangers of too early activity. Bonilla (8) noted in his series that the patients whose lesions became known during rest had a much more favorable prognosis than those whose lesions were detected during periods of physical activity.

It is believed that at least one year of good sanatorium care with complete bed-rest is the minimum amount of treatment which is advisable for a patient with primary pleural effusion. Periodic roentgenographic examination during the subsequent four years is of equal importance as recommended by Thompson (7). As noted above, a normal erythrocyte sedimentation rate within the first six months of rest does not necessarily preclude the subsequent development of a parenchymal lesion. Moreover, a normal value for the sedimentation rate is not a trustworthy guide by which to determine the proper duration of treatment.

The responsibility upon the physician, especially in civilian life, to regard an effusion as "probably tuberculous" and to initiate recognized treatment is tremendous. It entails study of possibilities versus probabilities in which often, if not invariably, the patient will make the final decision as indicated by the response and cooperation with treatment.

The degree of cooperation is usually directly proportional to the degree of certainty of diagnosis of the physician. The patient, when there is question or choice of diagnosis, will invariably apply the diagnosis of lesser consequence to his case.

It is relatively easy to practice didactic medicine in the Armed Forces. Among civilians, however, a period of long continued bed-rest creates a terrific economic problem. The financial catastrophe related to prolonged hospitalization frequently immediately overshadows the subsequent possibilities and probabilities of a course of disease to the patient. The physician must, with supreme effort, divorce himself from this influential factor in making the diagnosis and prescribing the necessary treatment.

There is still much to be learned about primary pleural effusions. A means of definitely establishing etiology and thereby removing the doubt from both the physician and the patient is urgently needed.

SUMMARY

1. A review of 100 cases of primary pleural effusion is presented. Twenty-one of the group developed pulmonary lesions and one developed renal tuberculosis within 6.2 months of onset.

2. The insidious onset of subjective symptoms was striking. Seventy-seven per cent of the series had symptoms for seven or more days prior to seeking medical aid and in ten instances the effusion was first detected on a routine roentgenographic examination.

3. It is apparently impossible to predict from the findings during the stage of the effusion whether pulmonary or other lesions will subsequently occur.

4. In the absence of satisfactory diagnostic tests, certain cases of pleural effusion must be classified as "probably tuberculous," although they may represent instances of primary atypical pneumonia. In general, such cases should be treated in the same way as the cases in which the tuberculous etiology is established.

5. The treatment recommended for primary pleural effusions consists of a period of sanatorium care (usually one year) followed by clinical, bacteriologic and roentgenographic examinations.

SUMARIO

La Importancia del Diagnóstico en el Derrame Pleural Primario

1. Esta reseña versa sobre 100 casos de derrame pleural primario. Veintiuno del grupo manifestaron lesiones pulmonares y uno manifestó tuberculosis renal en término de 6.2 meses de la iniciación.

2. Fué notable la insidiosa iniciación de los síntomas subjetivos. Setenta y siete por ciento de los enfermos habían tenido síntomas desde siete o más días antes de consultar al médico y en 10 casos se descubrió el derrame por primera vez al verificar un examen radiográfico de los corrientes.

3. Parece aparentemente imposible predecir por los hallazgos del período de derrame si se presentarán o no luego lesiones pulmonares o de cualquier otro género.

4. A falta de satisfactorias pruebas de diagnóstico, hay que clasificar ciertos casos de derrame pleural como "probablemente tuberculosos," aunque pueden representar neumonía atípica primaria. En general, esos casos deben ser tratados lo mismo que los de etiología tuberculosa establecida.

5. El tratamiento recomendado para los derrames pleurales primarios consiste en un período de asistencia sanatorial (por lo general un año), seguido de exámenes clínicos, bacteriológicos y radiográficos.

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PULMONARY EMPHYSEMA AND VENTILATION MEASUREMENTS IN ONE HUNDRED ANTHRACITE COAL MINERS WITH RESPIRATORY COMPLAINTS[1, 2]

HURLEY L. MOTLEY, LEONARD P. LANG AND BURGESS GORDON

INTRODUCTION

Anthracosilicosis (miner's asthma) is an occupational disease, characterized by silicotic pulmonary fibrosis, excessive retention of carbonaceous material and emphysema (1). Emphysema has been described as one of the most frequent gross findings, and the principal histologic change is a fibrous hyperplasia along lymph channels which occurs early and increases in certain areas to form nodules. Outstanding clinical features generally observed in anthracosilicosis include progressive dyspnea, accentuated by intercurrent infections, symptoms of failure of the pulmonary circulation and disability. In some cases the chest roentgenogram may be essentially normal, yet clinically there is a marked degree of disability. Emphasis has been placed on the diagnosis of silicosis from a correlation of all the facts (2), symptoms, signs, occupational history and laboratory and roentgen observations. In the present study information has been obtained on the ventilation impairment in anthracosilicosis from quantitative measurements of residual air, vital capacity, resting minute ventilation and maximal breathing capacity. These observations have been made on 100 unselected patients with respiratory complaints and a history of long exposure inside the mines. The pulmonary function and roentgenographic findings have been compared.

METHODS

The residual air was determined by the open circuit oxygen breathing method previously described (3). In the present study, however, a demand type regulator supplied the oxygen, replacing the constant flow regulator and rubber bag used in the original assembly. The subject was allowed to breathe 99.6 per cent oxygen for a seven minute period, during which all expired air was collected in a calibrated Tissot type spirometer. At the end of the seven minute period of oxygen breathing a sample was taken for the alveolar nitrogen determination. The dead space in the valve arrangement used for switching from air breathing to oxygen breathing and for alveolar nitrogen sampling was 65 cc. Duplicate residual air determinations were routine and required to check within 100 cc. in all cases except a few with a far advanced degree of emphysema where a tolerance of not over 5 per cent was permitted.

Maximal breathing capacity (MBC), vital capacity and supplemental or reserve air were determined with a modified Benedict-Roth metabolism apparatus (4). The predicted total lung volume was calculated from the height, age and sex (5). The bell of the apparatus has a diameter of 22.9 cm. and a volume of 13.5 L. The increased volume reduces the amplitude of the vertical movement of the bell with each breath and decreases the resistance for rapid

[1] From the Cardio-Respiratory Laboratory, Barton Memorial Division of Jefferson Medical College Hospital and the Department of Medicine of Jefferson Medical College.

[2] Investigation aided by a research grant of the Anthracite Health and Welfare Fund of Jefferson Medical College.

and deep breathing. The breathing resistance was further reduced by employing large tubing with an inside diameter of 2.9 cm. in conjunction with the high velocity directional valve used to prevent excessive accumulation of CO_2. Multiple measurements were obtained in every case, each being a twelve second run, with varying rates and depths of breathing. The values reported were the highest obtained. Measurements made on trained subjects with the above apparatus, which was designed to reduce resistance to a minimum for the MBC determinations, check closely with values obtained when employing the 100 L. Douglas bag and the high velocity directional valve. Two writing pens are used on the electrically driven (two speed) kymograph, one to record amplitude and rate of breathing and the other to add the total volume. The regression formula used for calculating the predicted values was: MBC L/min. = 86.5 − (0.522 × age in years) × B.S.A. (sq. m.) (6). All ventilatory volumes are measured as saturated gas at 37°C. and the prevailing barometric pressure.

Roentgenograms of the chest were taken at full inspiration and at full expiration in postero-anterior view. Routine fluoroscopy was done on all the patients.

All residual air measurements were made with the patients in a fasting and resting state lying supine and as flat as was comfortable for the individual. No medication was given to the patients. All MBC determinations were made in the standing position.

MATERIAL FOR STUDY

All of the patients were male anthracite coal miners with a long history of exposure to dust in mines. These miners were sent to the Barton Memorial Division of Jefferson Hospital for a study sponsored by the Anthracite Health and Welfare Research Fund of Jefferson Medical College. Patients were admitted to the Barton Memorial Hospital in order of the date of application for study, hence there was no selection by the laboratory staff except that subjects with proved pulmonary tuberculosis were omitted. However in 5 cases active tuberculosis was diagnosed after study (table 1). All but one of the patients complained of dyspnea. Chest pain, cough and expectoration, weakness, loss of weight and hemoptysis were the other most common complaints. In some patients dyspnea was present only during the course of minor respiratory infections, while in others there was a history of cyclic recurrence of the symptoms. All degrees of dyspnea were observed from the most profound, even during bedrest, to slight exertional dyspnea after exercise. There was no evidence of cardiac decompensation in this group at the time of study. However, two patients were known to have cardiac disease with electrocardiographic evidence of myocardial damage (table 1).

RESULTS

A quantitative indication of the degree of emphysema was obtained by expressing the residual air as per cent of the total lung volume (residual air + vital capacity). This is a physiological comparison of the relationship of the volume of residual air on the mixing and dilution factor with respect to the vital capacity and total lung volume. It is a more accurate measurement of pulmonary function impairment than the changes in residual air from the predicted, in which the wide variations in vital capacity are not correlated. Furthermore the total lung volume varied less from the predicted than either residual air or vital capacity measurements for the entire group (table 1). Accordingly the degree of emphy-

TABLE 1

Lung volume ventilation measurements, inside mine exposure time, and roentgenographic stage of silicosis in 100 cases of anthracosilicosis arranged in order of increasing residual air per cent of total lung volume

PATIENT	AGE	HEIGHT	BODY SURFACE AREA	EXPOSURE INSIDE MINES	X-RAY STAGE	RESIDUAL AIR		VITAL CAPACITY		MAXIMAL BREATHING CAPACITY		VENTILATION	BREATHING RESERVE OF MAXIMAL BREATHING CAPACITY	TOTAL LUNG VOLUME CHANGE FROM PREDICTED
						Observed	Total Lung Volume	Observed	Decrease From Predicted	Observed	Decrease From Predicted			
	I. Normal or no pulmonary emphysema													
	Yrs.	*cm.*	*sq.m.*	*Years*		*cc.*	*per cent*	*cc.*	*per cent*	*L./minute*	*per cent*	*L./minute*	*per cent*	*per cent*
J.C.	45	166	1.64	19	2	500	11.0	4,050	0.0	101	2.0	8.9	91.4	−13.8
J.P.	52	176	2.05	26	2	720	13.8	4,500	0.0	66	46.0	7.8	88.2	− 8.8
L.C.	40	173	1.84	18	3	879	16.6	4,400	0.0	94	21.4	6.4	93.2	− 9.0
W.R.	53	167	1.80	38	3	813	16.9	4,000	0.0	65	39.0	8.4	87.2	− 5.6
R.P.	53	170	1.70	25	3	543	19.4	2,280	43.0	43	57.3	6.5	85.0	−46.7
F.R.	54	171	2.08	40	2	898	19.6	3,680	9.7	107	12.4	10.0	90.6	−14.9
P.H.	44	172	1.72	28	3	975	20.2	3,682	6.0	81	29.0	6.9	91.2	−11.1
J.M.	44	175	1.89	25	2	1,091	20.4	4,270	0.0	103	5.0	6.7	92.3	− 5.0
H.Q.	47	170	1.74	30	2	1,181	20.8	4,500	0.0	112	0.0	7.9	93.0	+ 6.5
R.Z.	46	173	1.75	31	3	1,111	20.8	4,200	0.0	67	38.8	10.2	85.0	− 3.8
J.F.	57	174	1.95	36	2	1,254	21.8	4,500	0.0	96	13.7	6.8	92.8	+ 3.3
J.F.	41	170	1.80	20	3	1,219	22.3	4,250	0.0	90	30.0	9.7	89.2	+ 3.2
A.B.	61	170	1.75	26	3	887	22.5	3,045	24.0	50	48.0	7.0	86.0	−26.0
G.P.	44	165	1.78	24	1	1,033	23.1	3,440	8.3	87	23.5	8.1	90.6	− 8.4
Av.....	49	171	1.82	28		936	19.2	3,910	6.5	83	26.1	8.0	89.6	−10.0
	II. Slight degree of emphysema													
B.G.	52	164	1.63	30	2	1,280	25.5	3,730	0.0	97	0.0	9.7	90.0	+ 2.5
J.K.	48	172	1.88	20	2	1,405	26.0	4,000	8.0	38	67.0	8.8	75.8	− 5.7
H.S.	55	173	2.13	35	3	1,014	26.1	2,870	31.2	75	39.4	7.8	89.4	−29.5
P.V.	61	163	1.77	37	3	1,460	26.3	4,100	0.0	59	41.0	9.3	84.6	+15.3
J.S.	71	175	1.76	35	1	1,521	26.4	4,250	0.7	74	14.6	8.1	89.2	+ 2.0
G.K.*	65	158	1.54	37	2	1,123	26.8	3,115	8.5	47	42.0	13.3	71.7	− 4.8
M.E.	51	172	1.76	30	3	1,215	27.2	3,260	20.8	44	58.2	9.0	79.6	−19.7
A.Y.	51	168	1.69	26	1	1,454	28.1	3,720	0.0	68	31.0	8.4	87.7	+12.9
P.C.	43	157	1.60	23	3	1,023	29.2	2,490	25.2	48	53.0	7.5	83.2	−20.1
A.T.	67	169	1.81	47	3	1,469	30.1	3,400	14.1	67	28.7	10.1	85.2	− 7.1
C.S.	40	168	1.83	24	2	1,562	31.8	3,350	14.1	93	22.5	8.6	90.8	− 4.8
J.R.*	65	172	1.56	35	3	1,317	31.8	2,820	31.8	35	57.4	8.5	75.8	−24.0
J.G.	45	178	1.92	31	3	1,246	31.9	2,660	40.2	84	31.0	7.8	90.6	−33.6
F.S.	58	173	1.97	34	3	1,620	31.9	3,450	17.4	53	52.3	9.2	79.4	− 8.2
S.V.	51	171	1.96	37	1	1,547	32.0	3,300	18.9	88	17.7	11.8	86.6	− 9.6
J.A.	60	164	1.81	36	3	1,680	32.4	3,500	3.6	47	53.6	8.0	83.0	+ 7.9
A.S.	56	168	1.64	25	1	1,226	32.4	2,560	34.7	97	0.0	7.7	91.8	−26.9
A.S.	49	178	1.67	27	3	1,380	33.0	2,780	37.4	51	50.0	9.4	81.4	−29.0
L.T.	42	189	2.05	24	3	2,149	33.1	4,350	13.4	80	39.1	9.5	87.8	− 2.7

TABLE 1—*Continued*

PATIENT	AGE	HEIGHT	BODY SURFACE AREA	EXPOSURE INSIDE MINES	X-RAY STAGE	RESIDUAL AIR		VITAL CAPACITY		MAXIMAL BREATHING CAPACITY		VENTILATION	BREATHING RESERVE OF MAXIMAL BREATHING CAPACITY	TOTAL LUNG VOLUME CHANGE FROM PREDICTED
						Observed	Total Lung Volume	Observed	Decrease From Predicted	Observed	Decrease From Predicted			
II. Slight degree of emphysema—*Continued*														
	Yrs.	*cm.*	*sq.m.*	*Years*		*cc.*	*per cent*	*cc.*	*per cent*	*L./minute*	*per cent*	*L./minute*	*per cent*	*per cent*
J.V.	55	166	1.94	25	3	1,615	33.4	3,225	13.2	85	24.6	9.4	89.5	− 1.8
V.V.	54	168	1.73	33	3	1,700	34.4	3,230	20.8	43	57.4	7.2	83.8	− 9.5
P.Y.	45	181	1.84	30	3	1,578	34.8	2,960	35.0	70	40.0	10.3	85.4	−25.0
R.W.	60	173	1.74	40	3	1,073	34.9	2,080	50.2	81	16.0	9.0	89.0	−42.8
Av.....	54	170	1.78	31		1,420	30.8	3,270	19.1	66	36.3	9.0	85.0	−11.5
III. Moderate degree of emphysema														
S.M	58	178	1.87	32	3	1,267	35.3	2,340	47.5	81	22.8	10.4	86.7	−38.6
J.L.	64	175	1.80	35	3	1,405	35.8	3,520	44.5	50	47.9	7.7	84.7	−34.0
P.C.	56	167	1.71	35	2	1,710	36.2	3,010	21.6	81	17.2	8.5	88.8	− 9.7
F.M.	53	170	1.73	38	2	1,945	36.3	3,420	15.6	66	35.7	9.5	85.6	+ 1.0
T.M.	52	172	1.71	27	3	1,275	36.7	2,210	46.3	29	72.4	8.0	72.6	−36.0
J.B.†	53	173	1.93	43	2	2,080	36.8	3,600	12.6	84	26.3	10.7	73.3	+ 4.2
J.S.	45	162	1.58	24	3	1,100	37.3	1,850	48.4	24	76.0	7.9	67.0	−37.8
V.B.	43	180	1.74	25	3	1,282	37.5	2,140	53.0	43	61.8	7.9	81.4	−43.0
J.K.	55	161	1.69	28	3	1,278	37.6	2,120	40.0	27	73.5	6.9	87.3	−40.7
A.G.	59	179	1.88	42	3	2,267	37.8	3,740	16.7	56	46.5	7.3	87.2	+ 1.1
A.N.	72	159	1.69	28	3	1,824	38.6	2,910	19.7	54	35.2	9.7	82.0	− 1.0
D.R.	54	175	1.80	35	3	1,634	38.6	2,600	39.4	32	69.6	10.8	63.2	−25.2
A.S.	45	176	1.78	22	3	1,807	38.6	2,870	33.2	45	59.5	10.3	77.8	−18.6
M.K.	60	166	1.48	27	3	1,066	38.8	1,675	57.0	28	65.9	8.5	69.6	−47.2
T.P.	58	177	1.89	33	3	1,673	38.8	2,640	39.2	41	61.6	10.7	74.0	−25.6
A.H.	59	166	1.74	42	2	1,700	39.0	2,670	29.7	39	60.5	7.8	80.0	−13.3
C.B.	50	165	1.76	27	3	1,736	39.2	2,700	28.0	43	60.0	7.4	83.6	−11.8
C.H.	48	178	2.08	28	1	2,503	39.6	3,800	14.4	61	44.5	9.8	83.6	+ 7.6
P.A.	59	172	1.62	44	3	2,050	39.8	3,115	25.0	42	53.0	7.5	84.5	− 5.4
J.H.	51	166	1.68	36	3	1,810	39.8	2,740	46.0	85	18.9	8.6	89.4	−14.1
J.P.	61	167	1.64	45	2	1,590	41.0	2,290	40.6	48	58.0	7.8	83.4	−23.0
G.T.*	47	169	1.61	16	3	1,737	41.1	2,480	37.4	43	56.7	8.7	81.4	−19.6
K.K.	43	174	1.75	15	3	1,357	42.6	1,820	57.0	32	71.2	5.7	83.4	−42.3
J.U.	62	165	1.75	43	2	2,141	42.7	2,878	23.0	32	66.3	10.8	66.3	+ 1.0
J.C.	46	165	1.84	26	3	1,835	42.9	2,450	26.5	47	58.4	8.1	83.0	−17.6
J.P.	65	157	1.42	44	3	1,654	43.3	2,208	33.5	30	60.5	6.1	79.6	−13.7
B.D.	49	169	1.71	30	3	1,676	43.6	2,160	45.5	40	61.7	7.4	81.5	−27.5
A.H.	60	174	1.83	25	1	2,071	44.0	2,661	37.2	35	65.3	7.1	80.0	−15.5
E.M.	46	164	1.51	20	3	1,067	44.4	1,350	63.5	22	76.5	6.7	69.6	−50.6
J.S.	54	182	1.91	35	1	2,546	44.8	3,140	32.6	34	69.7	7.4	78.2	− 7.5
Av.....	54	170	1.73	32		1,703	39.6	2,637	35.8	46	55.1	8.4	79.6	−20.1

TABLE 1—*Concluded*

PATIENT	AGE	HEIGHT	BODY SURFACE AREA	EXPOSURE INSIDE MINES	X-RAY STAGE	RESIDUAL AIR		VITAL CAPACITY		MAXIMAL BREATHING CAPACITY		VENTILATION	BREATHING RESERVE OF MAXIMAL BREATHING CAPACITY	TOTAL LUNG VOLUME CHANGE FROM PREDICTED
						Observed	Total Lung Volume	Observed	Decrease From Predicted	Observed	Decrease From Predicted			
IV. Advanced degree of emphysema														
	Yrs.	*cm.*	*sq.m.*	*Years*		*cc.*	*per cent*	*cc.*	*per cent*	*L./minute*	*per cent*	*L./minute*	*per cent*	*per cent*
J.V.	57	168	1.70	36	2	2,212	45.2	2,680	31.0	42	56.7	7.4	81.6	− 5.2
C.T.	53	174	1.92	34	2	2,410	46.5	2,780	34.5	30	73.5	8.9	70.3	− 7.3
L.M.*	42	169	1.54	24	3	1,626	48.2	1,750	55.2	35	65.0	10.9	68.6	−34.6
H.F.	62	175	1.67	25	3	1,970	48.3	2,120	50.7	25	72.2	7.7	69.2	−28.0
J.Y.*	63	158	1.54	37	3	2,325	48.4	2,480	30.3	29	64.4	8.1	72.0	+ 2.0
S.F.	64	171	1.61	42	3	1,869	48.7	1,970	52.3	23	73.2	7.9	65.7	−29.9
J.B.	42	172	1.85	27	3	2,047	48.8	2,150	47.8	42	64.8	8.5	77.7	−23.0
J.M.	48	167	1.85	23	3	2,373	49.0	2,450	37.0	26	77.0	7.7	70.4	− 5.4
J.K.	62	173	1.63	41	3	2,494	51.0	2,400	42.9	30	65.8	10.6	64.6	−11.6
J.N.	46	169	1.64	25	3	1,418	51.0	1,360	65.0	26	74.2	8.4	69.2	−46.1
G.S.	40	175	1.90	23	3	3,440	51.0	3,290	23.2	56	54.4	9.0	84.0	+18.9
J.B.	53	175	1.86	29	2	2,898	51.8	2,700	37.0	32	67.0	7.3	77.2	− 2.0
A.J.	47	171	1.73	26	3	2,421	52.0	2,230	46.2	27	80.0	7.5	74.0	−13.9
V.P.	44	176	1.68	24	3	2,370	52.0	2,280	27.4	27	74.8	6.6	75.6	−20.7
J.S.	51	164	1.66	20	3	1,547	52.5	1,400	63.2	18	81.6	6.4	66.8	−41.3
W.R.	53	167	1.82	32	3	3,015	53.7	2,610	35.6	31	71.0	8.9	71.4	+ 5.0
G.C.	46	182	1.90	23	3	2,199	54.3	2,620	43.6	34	71.0	5.5	84.0	−21.8
F.M.	57	178	1.69	30	3	2,933	55.8	2,420	54.5	74	22.5	10.2	86.2	− 8.8
Av.....	52	171	1.73	29		2,305	50.4	2,315	43.3	34	67.0	8.2	73.8	−15.2
V. Far advanced degree of emphysema														
J.S.	45	168	1.53	24	3	1,753	55.8	1,410	64.0	22	77.5	7.0	68.0	−38.7
R.O.	57	174	1.71	37	3	2,068	56.6	1,598	62.3	24	75.4	6.1	71.5	−34.5
L.Q.	51	177	1.72	25	3	2,250	57.0	1,689	61.6	21	79.0	6.3	70.0	−32.3
H.M.	60	173	1.88	38	2	3,117	57.5	2,335	44.3	29	71.8	8.3	71.4	− 1.4
R.S.	57	164	1.54	31	2	3,330	57.5	2,410	40.0	29	66.0	8.6	70.4	+17.0
G.P.	51	172	1.77	36	1	2,777	57.8	2,020	51.0	27	74.6	7.6	70.4	−12.0
J.B.	63	175	1.71	43	3	2,532	59.0	1,745	59.2	26	72.2	5.2	79.6	−24.4
J.G.	60	177	1.76	34	1	2,319	59.3	1,620	62.8	15	85.0	5.3	64.6	−31.7
N.C.	64	169	1.67	37	3	3,867	60.0	2,570	35.0	36	59.5	11.7	67.7	+22.6
E.S.	38	172	1.70	14	3	2,997	62.6	1,685	59.0	11	89.0	7.0	36.4	−12.1
W. H.†	64	170	1.98	55	2	2,842	62.8	1,700	57.5	40	62.0	8.3	80.0	−14.3
W.B.	47	176	1.73	26	1	3,988	64.3	2,220	48.8	35	67.5	10.0	71.5	+ 8.4
A.J.	59	186	1.78	43	3	2,934	65.0	1,575	56.5	21	78.8	6.9	67.6	−27.5
M.M.	65	158	1.50	56	1	2,561	65.0	1,380	64.0	27	66.4	7.7	70.4	−22.0
F.S.	41	175	1.74	21	3	3,260	65.2	1,740	60.0	16	86.0	7.5	53.0	−13.4
Av.....	55	172	1.71	35		2,836	60.3	1,844	55.1	25	74.0	7.6	67.5	−14.4

* Diagnosis of tuberculosis made from examination of sputum and secretions.

† Patient had cardiac disease with electrocardiographic evidence of myocardial damage.

sema was classified in five groups based on the residual air per cent of total lung volume as described below. The volume of residual air normally constitutes 25 per cent or less of the total lung volume. When such values are obtained the lungs as a whole are physiologically not emphysematous, although there may be small scattered or localized areas of bullae or blebs which are insignificant in their contribution to the pulmonary functional impairment by increasing the mixing and dilution factor. When the residual air occupies 25 to 35 per cent of the total lung volume a slight degree of emphysema is present, which again is not generally of sufficient magnitude to produce symptoms from the emphysema factor *per se*, that is, the mixing and dilution factor imposed by the increased volume of residual air. An occasional exception is represented by the patient with a marked decrease in vital capacity. If, however, the residual air is 35 to 45 per cent of the total lung volume, emphysema of a moderate degree exists. If the residual air is proportionately greater (45 to 55 per cent), the emphysema is advanced, and is far advanced when the residual air represents more than 55 per cent of total lung volume. In general, for the emphysema alone to alter pulmonary function significantly, the residual air must occupy 35 per cent or more of the total lung volume.

The data of the 100 cases are presented in table 1, and are arranged in five groups with respect to the severity of the emphysema. In each group the individual cases are listed in order according to the increasing percentage of total lung volume occupied by the residual air. The average values for each group are given in table 2, which is a summary of table 1.

The duration of exposure to dust inside the mines, as reported by the patient, ranged from 20 to 45 years, with the exception of four cases. There was no relationship between the length of exposure and the degree of pulmonary emphysema present (tables 1 and 2).

In the group of cases with a history of 20 to 25 years exposure (table 1), there were 25 patients. In 9 the degree of emphysema was advanced or far advanced, in 6 it was moderate and in 10, or 40 per cent, the emphysema was insignificant. The findings were similar in the group with a history of 35 to 40 years of inside exposure. Six of these 23 patients had an advanced or far advanced degree of emphysema, 6 had a moderate degree and 11, or 47.8 per cent, had insignificant emphysema. In this series one case with a history of 14 years of exposure had a far advanced degree of emphysema, but another case with 47 years of exposure had only a slight degree of emphysema. Two other patients with histories of exposure inside the mines of 55 and 56 years, respectively, had emphysema of a far advanced degree.

Figure 1 shows the relationship of age and residual air, expressed as per cent of total lung volume. It will be noted that 14 per cent of the cases had no emphysema and 23 per cent had only a slight degree of emphysema, making a total of 37 per cent without a significant degree of emphysema. However, 63 per cent of the cases did have a significant degree of emphysema distributed as follows: 30 moderate; 18 advanced; and 15 far advanced. Figure 1 reveals that the ages are, for the most part, between 40 and 65 years, and that all degrees of emphysema occur in all age groups. For example, of 37 in the 40 to 50 year age

group, a significant degree of emphysema was present in 59.4 per cent of the cases and an advanced degree in 32.4 per cent. In the 50 to 60 year age group, (38 cases) 63.2 per cent had a significant degree of emphysema and 28.9 per cent an advanced degree. In the group 60 years of age and above, (24 cases) 66.7 per cent had a significant degree of emphysema and 37.5 per cent an advanced degree.

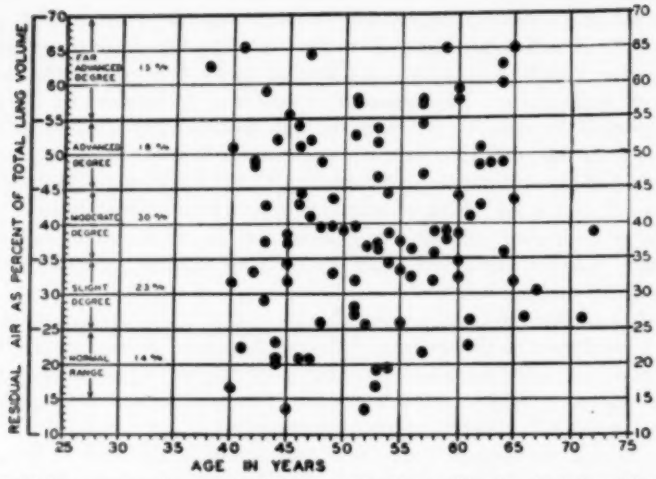

FIG. 1. Pulmonary emphysema in 100 cases of anthracosilicosis. Relationship between age in years and degree of pulmonary emphysema (as indicated by expressing the residual air as per cent of total lung volume on the ordinate) in 100 cases of anthracosilicosis. Each dot represents one patient. Note the occurrence of all degrees of emphysema in all age groups (40 to 65 years). In 14 per cent of the cases there was no emphysema and in 23 per cent only a slight degree of emphysema.

One patient, (ES table 1), 38 years of age with a 14 year history of exposure inside the mines had a far advanced degree of emphysema. It should be noted that 76 per cent of the patients studied were under 60 years of age and 31.6 per cent of these had an advanced and disabling degree of pulmonary emphysema.

Alveolar nitrogen: The alveolar nitrogen per cent after seven minutes of 99.6 per cent oxygen breathing was averaged by groups as shown below:

GROUPS	TOTAL NUMBER OF CASES	AVERAGE ALVEOLAR NITROGEN PER CENT	RANGE OF ALVEOLAR NITROGEN PER CENT
1. No emphysema	14	2.05	(1.00 to 4.22)
2. Slight emphysema	23	2.18	(0.81 to 4.38)
3. Moderate emphysema	30	3.40	(1.16 to 11.90)
4. Advanced emphysema	18	4.82	(1.44 to 9.65)
5. Far advanced emphysema	15	5.90	(2.67 to 11.80)

The average alveolar nitrogen per cent in the five groups shows a progressive increase as the degree of emphysema increases; however, the individual variations in each group are large.

Relationship between vital capacity and residual air: The relationship between vital capacity and the residual air expressed as per cent of total lung volume may be seen in figures 2 and 3. In general the decrease in vital capacity for the greater number of cases varied from 30 to 65 per cent below the predicted value. There

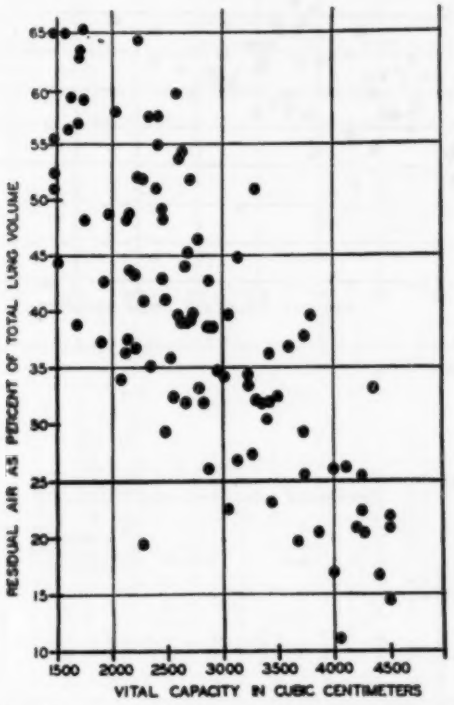

FIG. 2. Relationship between vital capacity and the degree of emphysema.

was poor correlation between vital capacity and the pulmonary emphysema present, the individual variations between cases with similar degrees of emphysema being great (figure 2). A vital capacity of 2,500 cc. may occur in the presence of no emphysema or in far advanced emphysema (figure 2). The average values for the groups classified by the degree of emphysema present (table 2 and figure 4), reveal a progressive decrease in the vital capacity as the residual air per cent of total lung volume increases.

The vital capacity (VC) data, given in table 1 and figure 3 may be further

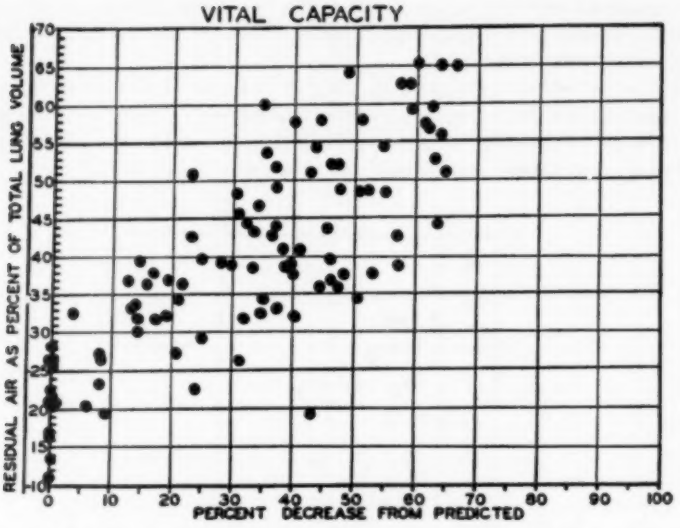

FIG. 3. Relationship between the per cent decrease in vital capacity from the predicted values and the degree of emphysema.

TABLE 2

Averages of values presented in table 1

GROUP	NUMBER CASES	AGE	HEIGHT	BODY SURFACE AREA	EXPOSURE INSIDE MINES	RESIDUAL AIR		VITAL CAPACITY		MAXIMAL BREATHING CAPACITY		VENTILATION	BREATHING RESERVE OF MAXIMAL BREATHING CAPACITY	TOTAL LUNG VOLUME CHANGE FROM PREDICTED
						Observed	Total Lung Volume	Observed	Decrease From Predicted	Observed	Decrease From Predicted			
		Yrs.	*cm.*	*sq. m.*	*Yrs.*	*cc.*	*per cent*	*cc.*	*per cent*	*L. per minute*	*per cent*	*L./minute*	*per cent*	*per cent*
I	14	49	171	1.82	28	936	19.2	3,910	6.5	83	26.1	8.0	89.0	−10.0
II	23	54	170	1.78	31	1,420	30.8	3,270	19.1	66	36.3	9.0	85.0	−11.5
III	30	54	170	1.73	32	1,703	39.6	2,637	35.8	46	55.1	8.4	79.6	−20.1
IV	18	52	171	1.73	29	2,305	50.4	2,315	43.3	34	67.0	8.2	73.8	−15.2
V	15	55	172	1.71	35	2,836	60.3	1,844	55.1	25	74.0	7.6	67.5	−14.4

Group I. Normal or no pulmonary emphysema.
Group II. Slight degree of emphysema.
Group III. Moderate degree of emphysema.
Group IV. Advanced degree of emphysema.
Group V. Far advanced degree of emphysema.

grouped for analytical study based on the decrease from the predicted values as follows:

(1) Degree of emphysema not significant, 37 cases.
- 19 cases (51.4 per cent).....Decrease in VC 10 per cent or less
- 10 cases (27.0 per cent).....Decrease in VC 10 to 30 per cent
- 8 cases (21.6 per cent).....Decrease in VC 30 to 50 per cent

(2) Degree of emphysema significant, 63 cases.
- 10 cases (15.9 per cent).....Decrease in VC 10 to 30 per cent
- 32 cases (50.8 per cent).....Decrease in VC 30 to 50 per cent
- 11 cases (17.4 per cent).....Decrease in VC 50 to 60 per cent
- 10 cases (15.9 per cent).....Decrease in VC 60 to 70 per cent

(3) In the group of 33 patients with an advanced and disabling degree of emphysema, 16 (48.5 per cent) had a vital capacity which was decreased less than 50 per cent from the predicted value.

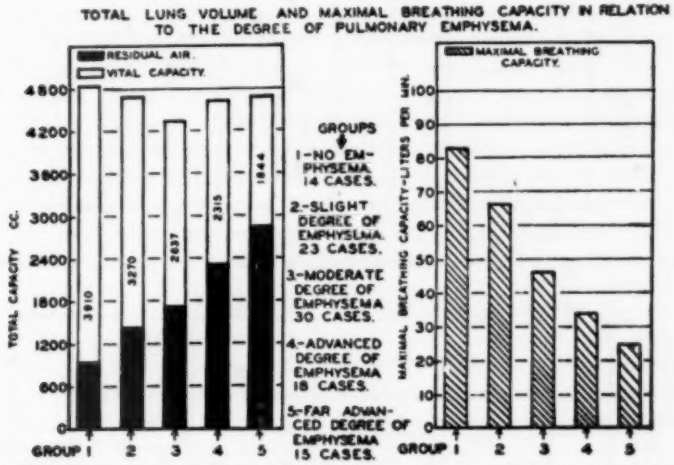

FIG. 4. Total lung volume and maximal breathing capacity in relation to the degree of pulmonary emphysema.

Maximal breathing capacity: The maximal breathing capacity (MBC) was measured at the same time as the vital capacity. The relationship between MBC and the degree of pulmonary emphysema is presented in figures 5 and 6. There is a better correlation between the degree of pulmonary emphysema present and the reduction in MBC observed than was found to exist between vital capacity and emphysema. In 56 cases the MBC was reduced 50 to 80 per cent from the predicted value and in 25 cases the decrease was 70 per cent or more from the predicted value (figure 6). The decrease in MBC from the predicted value, as shown in figure 6 and table 1, may be similarly grouped for analysis as was the vital capacity:

(1) Degree of emphysema not significant, 37 cases.
- 5 cases (13.5 per cent).....Decrease in MBC 10 per cent or less
- 11 cases (29.8 per cent).....Decrease in MBC 10 to 30 per cent

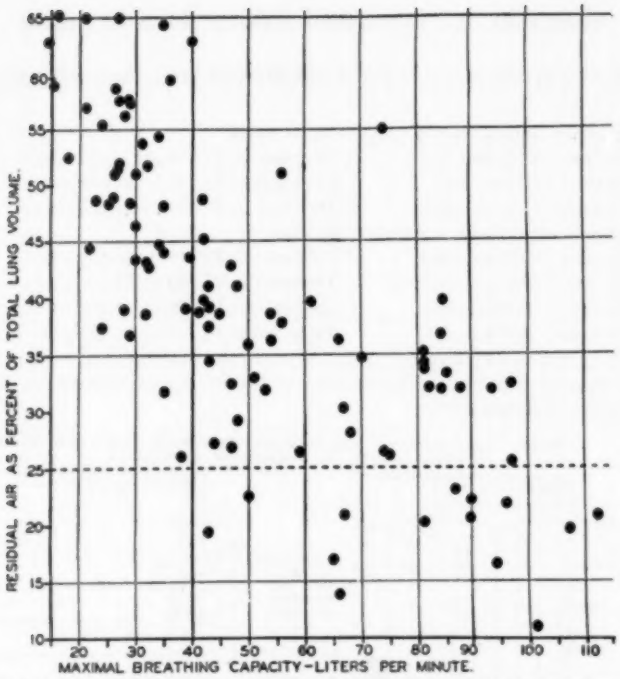

FIG. 5. Relationship between maximal breathing capacity and the degree of emphysema.

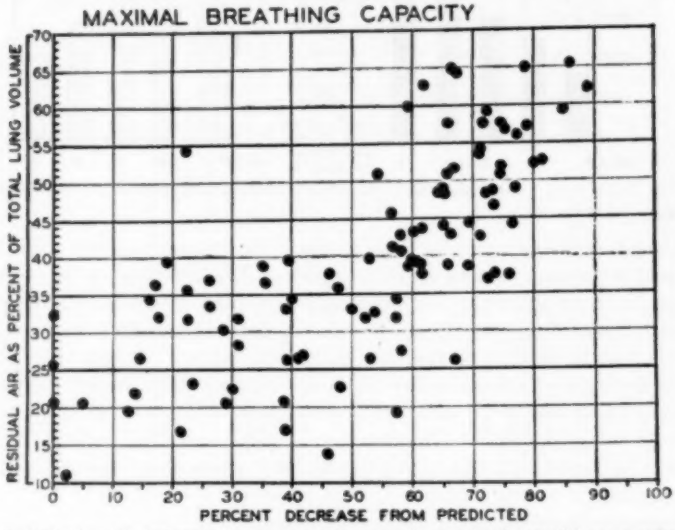

FIG. 6. Relationship between the per cent decrease in maximal breathing capacity from the predicted and the degree of emphysema. Note the greater decrease as compared to vital capacity in figure 3.

12 cases (32.4 per cent).....Decrease in MBC 30 to 50 per cent
8 cases (21.6 per cent).....Decrease in MBC 50 to 60 per cent
1 case (2.7 per cent).....Decrease in MBC 60 to 70 per cent

(2) Degree of emphysema significant, 63 cases.

5 cases (7.9 per cent).....Decrease in MBC 10 to 30 per cent
5 cases (7.9 per cent).....Decrease in MBC 30 to 50 per cent
9 cases (14.3 per cent).....Decrease in MBC 50 to 60 per cent
19 cases (30.3 per cent).....Decrease in MBC 60 to 70 per cent
20 cases (31.7 per cent).....Decrease in MBC 70 to 80 per cent
5 cases (7.9 per cent).....Decrease in MBC 80 to 90 per cent

(3) In the group of 33 patients with an advanced and disabling degree of pulmonary emphysema, all except one had 50 per cent or greater decrease in MBC.

In general, MBC shows a much better correlation with the disability produced by the pulmonary emphysema than is shown by the vital capacity. Although in some instances the variations in individual cases with the same degree of emphysema are large, they are not as great as are seen in the vital capacity measurements (figures 2 and 5). The average for the five groups (table 2, figure 6), shows a smooth progressive decrease in MBC as the residual air increases and the vital capacity decreases. If the MBC is decreased 60 per cent or more from the predicted value or if the actual measurement for men is 40 L. per minute, or less, the degree of emphysema present is usually significant (figures 5 and 6).

Hyperventilation: Hyperventilation was present in all groups (tables 1 and 2). A few patients in each group exhibited marked hyperventilation, in some instances resulting from apprehension and in others as a compensatory response to the emphysema. Although the resting minute ventilation has limited prognostic value as a single measurement, it is useful in determining the breathing reserve. The breathing reserve expressed as per cent of MBC was 89.6, 85.0, 79.6, 73.8 and 67.5 respectively for the five groups (tables 1 and 2). The breathing reserve when expressed in this manner shows a fair correlation with the degree of emphysema present (figure 7). If the breathing reserve was 70 per cent or less of the MBC, the degree of emphysema was significant but was insignificant if the breathing reserve was 90 per cent or more of the MBC.

The total lung volume was decreased in 81 out of 100 cases. The most marked decrease, an average of 20 per cent, was in the third group with a moderate degree of emphysema (figure 4 and table 2). In this group a proportionally greater decrease in vital capacity and smaller increase in residual air were present as compared to the other groups. Patients with an advanced degree of pulmonary emphysema apparently have developed more compensatory emphysema with a resulting smaller decrease in total lung volume. Why some patients develop so much more compensatory emphysema than others is not known. The extent of the emphysema in this group at least was not apparently related to age, height, weight, or length of exposure in mines.

Roentgenographic findings: The chest roentgenograms were classified according to the descriptions of Pancoast and Pendergrass (7) (table 1). In this classification the first stage is characterized by increase in the size and density of the hilar

lymph nodes, perivascular thickening outward toward the pleura, and a slight fine mottling in the parenchyma; the second stage by typical nodular round and

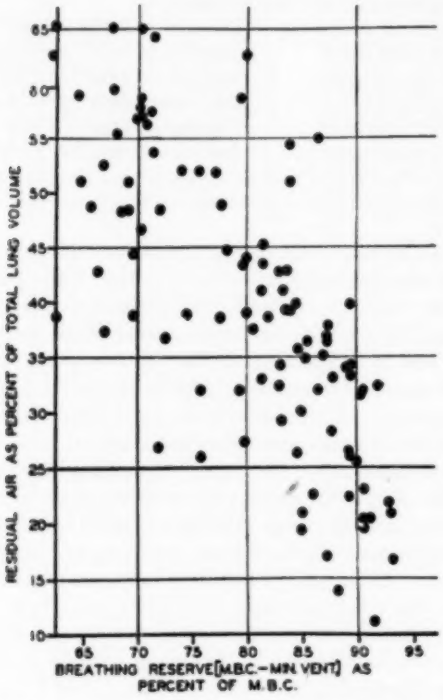

FIG. 7. Relationship between breathing reserve and the degree of emphysema.

TABLE 3

Stage of silicosis based on roentgenogram, and degree of pulmonary emphysema as determined from measurements of residual air and total lung volume

DEGREE OF EMPHYSEMA	TOTAL NUMBER OF CASES	FIRST STAGE	SECOND STAGE	THIRD STAGE
1. None	14	1	5	8
2. Slight	23	4	4	15
3. Moderate	30	3	6	21
4. Advanced	18	0	3	15
5. Far advanced	15	4	3	8

oblong shadows of soft even density from 2 to 6 mm. in diameter radiating from the hilus; and the third stage by the presence of shadows larger than 6 mm. in diameter, more numerous and with coalescence into aggregates. In this series of 100 cases, 67 were classified as third stage, 21 as second stage, and 12 as first

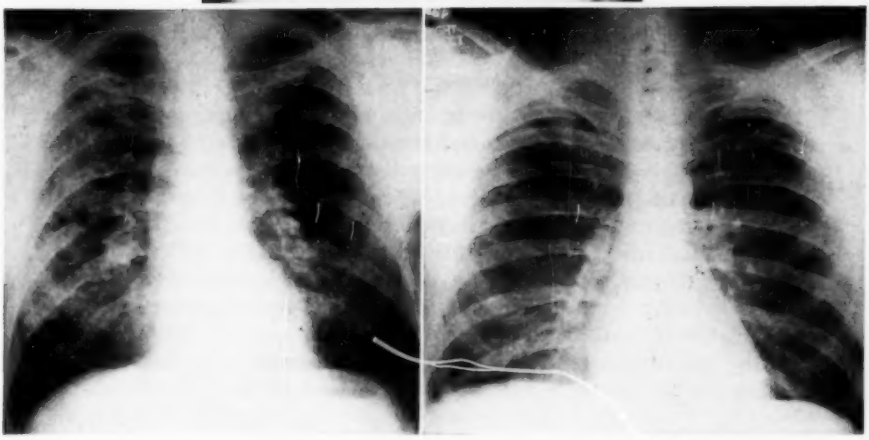

FIG. 8. (Upper) Typical roentgenogram of the chest taken at full inspiration in a case with far advanced emphysema. History of 43 years inside mine work. Present complaints: marked dyspnea and weakness, slight cough and expectoration and 55 lb. weight loss. Age 63. Residual air 2,532 cc., vital capacity 1,745 cc., residual air equals 59 per cent of total lung volume, and maximal breathing capacity 26 L. per minute. Good correlation between roentgenographic findings and studies of pulmonary function.

FIG. 9. (Lower left) A case illustrating poor correlation between roentgenographic findings (inspiratory film) and studies of pulmonary function. History of 20 years inside mine work. Present complaints: dyspnea on effort, cough and expectoration, weakness and 15 lb. weight loss. Age 41. Residual air 1,219 cc., vital capacity, 4,250 cc., residual air equals 22.3 per cent of total lung volume, and maximal breathing capacity 90 L. per minute. No emphysema present.

FIG. 10. (lower right) Another example showing discrepancy between roentgenographic findings (inspiratory film) and the studies of pulmonary function. History of 28 years inside mine work. Present complaints: dyspnea, marked cough and expectoration and upper chest pain. Age 48. Residual air 2,503 cc., vital capacity 3,800 cc., residual air equals 39.6 per cent of total lung volume, maximal breathing capacity 61 L. per minute. Moderate degree of emphysema present.

stage. In a few of the cases classified as first stage silicosis there was question as to whether or not the degree of exaggeration of the lung marking was within normal limits. Four of the 12 cases with first stage silicosis had a far advanced degree of emphysema. There was no apparent relationship between the stage of silicosis, as estimated from roentgenograms, and the degree of pulmonary emphysema (table 3).

The 67 cases of third stage silicosis present two points of interest: (*1*) the lack of correlation between the roentgenographic findings and the emphysema; and (*2*) the distribution relationship between the emphysema and the total number of cases in each group. In the cases with a far advanced degree of emphysema and third stage silicosis, the chest roentgenogram was satisfactory for predicting the degree of emphysema and the limitation in maximal breathing capacity (figure 8). However, in other cases a wide discrepancy was observed (figures 9 and 10). The movement of the diaphragm on fluoroscopy and as seen on inspiratory and expiratory films and changes in illumination of the lungs between inspiration and expiration were most helpful in predicting the degree of emphysema present. In many cases, however, the predicted values were erroneous.

DISCUSSION

In 100 anthracite coal miners the maximal breathing capacity, vital capacity, minute ventilation, breathing reserve, duration of exposure in mines, and the roentgenographic changes have been correlated with the degree of pulmonary emphysema. The maximal breathing capacity (MBC) was observed to show the best single correlation. If the maximal breathing capacity was less than 40 L. per minute, the emphysema present was a significant factor in the impairment of pulmonary function. Vital capacity as a single measurement was of limited value in predicting the extent of the emphysema, and could not be relied upon as a quantitative measure of pulmonary functional impairment. In the present study the greatest value of vital capacity determinations was in the calculation of total capacity. The decrease in vital capacity below the predicted value was consistently less than was the reduction in maximal breathing capacity, a relationship also observed by others (8). No constant relationship exists between vital capacity and maximal breathing capacity, however, and, with few exceptions, the MBC measurements were a more reliable indication of the degree of disability than were the deviations in vital capacity. In the present study maximal breathing capacity was the best single test of the ventilation factor of pulmonary function. This results from the facts that MBC is concerned with the movement of the diaphragm, the intercostals, and other accessory muscles of respiration, the patency of the tracheobronchial pulmonary airway, the elastic property of lung tissue, and neuromuscular coordination. Maximal breathing capacity measurements are simple to perform and offer a practicable test of pulmonary function for mass examinations. If MBC measurements are used routinely along with the chest roentgenogram, the efficiency of the search for early evidence of silicosis should be greatly improved.

There was no demonstrable relation between exposure time in the mines and the degree of emphysema present. The findings in the present study suggest

that individual susceptibility to exposure of coal mine dust varies and unknown intrinsic factors may exert an influence on the degree of pulmonary disability that follows. Bamberger (9) has reported that, in a group of miners working under the same conditions at the same time, one may develop linear exaggeration of a mild degree, whereas another will develop far advanced nodular silicosis. The condition of the ciliated epithelium (10) may be responsible for the lack of a normal degree of protection against dust invasion. Decreased motility of the cilia in certain persons impairs the removal of inhaled particles. The exposure time as given by the patient has a limited value, although in the present study as exact a history as possible of the total time inside the mines was sought. As many accurate measurements of the degree of emphysema have been made, the observations reported in table 1 suggest the presence of an individual susceptibility factor. For example, case F. R., age 54 (group 1, table 1), with a 40 year history inside the mines had no emphysema, while case F. S., age 41 (group 5), with a 21 year history inside the mines had a far advanced degree of emphysema. Although the concentration of dust in the mines varies widely, it is unlikely, even if the exact amount of dust inhaled could be ascertained, that it could be correlated with the degree of emphysema present in this series of 100 cases.

The findings indicate that practically all of the subjects hyperventilated, but there was no significant correlation between the extent of hyperventilation and the degree of emphysema. Hyperventilation is a compensatory mechanism, however, and during the early stages of the process may be adequate until loss of elasticity of the lungs and obstruction markedly decrease MBC and VC. The minute ventilation alone was not related to the extent of pulmonary disability. In most cases the total lung volume was decreased. Nineteen per cent of the cases showed an increase, however, and in a few there was no significant change. Compensatory emphysema was present in some cases and absent in others. Some of the patients with flat chests had an advanced degree of emphysema, probably indicating a more rapid development of the emphysema and the onset of the process later in life than in the case of the typical "barrel" shaped chest of the asthmatic with a far advanced degree of emphysema.

The roentgenographic findings alone do not permit a proper evaluation of the impairment of pulmonary function in many cases. Extensive deposits of silica may be demonstrated on the roentgenogram when the pulmonary function is only moderately altered, while in other cases with minimal findings on the roentgenogram, the pulmonary function is greatly impaired. In a considerable number of cases even the degree of emphysema present is difficult to approximate from the roentgenogram alone.

As 14 per cent of the cases in this series had a residual air less than the normal predicted, and 23 per cent had only a slight increase in the residual air per cent of total lung volume, pulmonary emphysema could not be assigned as the basis of the respiratory difficulty. Furthermore, in most instances those subjects with an insignificant amount of emphysema did not have a reduction in MBC of sufficient degree to account for the symptoms presented.

At the present time the studies are being extended to investigate the nature of different types of impairment of pulmonary function including the transfer

of O_2 and CO_2 between the alveoli and arterial blood. Preliminary findings indicate that the fibrosis present in some cases of anthracosilicosis, although not producing a significant degree of emphysema, interferes with the uniform aeration of the alveoli (the distribution factor (11, 12)). Consequently an increased percentage of alveoli are poorly ventilated with a resulting increase in the mean pressure gradient of pO_2 between the alveoli and the arterial blood. Distribution, one of the factors contributing to the alveolar-arterial pO_2 gradient, may be defined as: (*1*) the variations in alveolar pO_2 in different parts of the lungs; and (*2*) the ratio of alveolar ventilation to alveolar perfusion. Also the fibrosis obliterates the blood supply to alveoli, so that areas of the lung are ventilated but not perfused, thus increasing the physiological dead space and reducing the efficiency of O_2 removal per liter of ventilation. Furthermore, studies with high and low levels of oxygenation indicate that the increased pO_2 gradient between the alveoli and arterial blood is primarily one of distribution and not a diffusion difficulty (increased resistance to passage of oxygen through the pulmonary membrane). The pulmonary functional impairment of distribution described above may produce marked arterial oxygen unsaturation at rest even in the absence of emphysema and with a normal maximal breathing capacity. An accurate clinical evaluation of the disability in such a patient is very unlikely when the roentgenographic findings are minimal.

The compensatory mechanism for the mixing and dilution problem imposed by the increased volume of residual air is hyperventilation. The extent of this response varies widely, so that compensation is good in some patients and poor in others with the same amount of emphysema. Fibrosis and loss of elasticity of the chest wall structures and lungs restricts the amount of hyperventilation possible without dyspnea. The dyspnea level varies widely, a fact which explains the observations that the severity of respiratory symptoms are not an accurate measure of the relationship between the residual air and the total lung volume.

SUMMARY

The degree of pulmonary emphysema has been evaluated physiologically, and ventilation measurements obtained, in 100 unselected cases of anthracosilicosis with pulmonary symptoms and a long history of exposure to mine dust.

A quantitative indication of the degree of emphysema was obtained by expressing the residual air as per cent of the total lung volume. On the basis of this value all cases were classified in five groups as follows: (*1*) no emphysema (25 per cent or less); (*2*) slight degree of emphysema (25 to 35 per cent); (*3*) moderate degree of emphysema (35 to 45 per cent); (*4*) advanced degree of emphysema (45 to 55 per cent); and (*5*) far advanced degree of emphysema (65 per cent or more).

No relationship existed between the history of length of exposure to mine dust and the degree of pulmonary emphysema present. Moreover, there was no apparent relationship between the stage of silicosis, as determined from the roentgenogram, and the degree of pulmonary emphysema present. Most of

the subjects were between 40 and 65 years of age and all degrees of emphysema were present in all age groups.

The degree of emphysema present was better correlated with the maximal breathing capacity than with the vital capacity. The decrease from the predicted value was consistently greater for maximal breathing capacity than vital capacity. If the maximal breathing capacity was below 40 L. per minute or decreased 60 per cent or more from the predicted, the amount of emphysema present was significant in producing impairment of pulmonary function.

The routine use of maximal breathing capacity measurements along with the chest roentgenogram should enhance the efficiency of the search for early evidence of silicosis.

Measurements of resting minute ventilation revealed that hyperventilation was consistently present. The average values for breathing reserve in the different groups show a progressive decrease as the degree of emphysema increases although wide individual variations exist.

Pulmonary emphysema accounts for part of the impairment of pulmonary function in anthracosilicosis. In a considerable number of cases, however, other factors must be responsible because the amount of emphysema present is not significant.

SUMARIO

Enfisema Pulmonary Mediciones de la Ventilación en Cien Mineros de Carbón de Antracita con Síntomas del Aparato Respiratorio

En 100 casos no seleccionados de antracosilicosis con síntomas pulmonares y prolongada historia de exposición al polvo de minas, se valuó fisiológicamente la intensidad del enfisema pulmonar y se obtuvieron mediciones de la ventilación.

Expresando el aire residual en por ciento del volumen pulmonar total, se obtuvo una indicación cuantitativa del grado del enfisema. A base de esa cifra, todos los casos fueron clasificados en cinco grupos, a saber: (1) sin enfisema (25 por ciento o menos); (2) enfisema leve (25 a 35 por ciento); (3) enfisema moderado (35 a 45 por ciento); enfisema avanzado (45 a 55 por ciento), y enfisema muy avanzado (65 por ciento o más).

No hubo relación entre la historia de la duración de la exposición al polvo de mina y la intensidad del enfisema pulmonar presente. Tampoco existía aparentemente entre el período de la silicosis, determinado por la radiografía, y la intensidad del enfisema pulmonar. La mayor parte de los sujetos tenían de 40 a 65 años de edad, observándose en todos los grupos etarios los diversos grados del enfisema.

La intensidad del enfisema presente se correlacionó con la capacidad respiratoria máxima mejor que con la capacidad vital, siedno la disminución de la cifra anticipada constantemente mayor para la primera que para la segunda. Si la capacidad respiratoria maxima era inferior a 40 L. por minuto o quedaba 60 por ciento o más por debajo de lo anticipado, la intensidad del enfisema presente afectaba significativamente la función pulmonar.

El empleo sistemático de las mediciones de la capacidad respiratoria máxima,

junto con la radiografía torácica, debe acrecentar la eficacia de la pesquisa de signos temperanos de silicosis.

Las mediciones de la ventilación por minuto en reposo revelaron constantemente la presencia de hiperventilación. Las cifras medias de la reserva respiratoria en los diversos grupos muestran, aunque existen variaciones individuales, una disminución gradual a medida que se acentúa el enfisema.

El enfisema pulmonar explica parte de la reducción de la función pulmonar en la antracosilicosis, pero en una considerable proporción de casos, deben intervenir otros factores por no revestir importancia el enfisema presente.

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MANAGEMENT OF TUBERCULOSIS IN PSYCHOTIC PATIENTS[1, 2]

LOUIS O. LAMBIOTTE, EDWARD L. WASHINGTON AND GEORGE S. BOZALIS

INTRODUCTION

The purpose of this paper is to instill optimism and to eliminate some of the pessimism that has often pervaded the literature regarding the problems of tuberculosis that exist in most large mental institutions. The fact that an appreciable number of psychotics make at least a partial recovery and return to their families and home communities and the problem of control of the disease in the institution make a more active approach desirable.

There have been many articles in reference to tuberculosis among the mentally ill (1, 2, 3, 4). However, reference to the literature has not been successful in yielding much information in regard to treating these patients. In the majority of instances an attitude of pessimism has prevailed. This is particularly true in regard to collapse therapy and thoracic surgery. For example, Wicks (5) states "it is rather doubtful whether any of the more radical types of chest surgery (with the possible exception of intrapleural pneumonolysis) should be attempted in a tuberculosis mental unit." Leonidoff (6) states "pneumothorax is unsuitable for the mentally ill patient". Although it is not intended to minimize the difficulties involved in treating psychotic patients with pulmonary tuberculosis, the writers believe that a more optimistic attitude is warranted. To support that contention is the purpose of the present report which is based on experiences with 100 cases of pulmonary tuberculosis treated at the Veterans Administration Hospital, North Little Rock, Arkansas, during the past two years. Although the period of observation has been of insufficient length to permit statistically valid conclusions as to the final result of treatment, it is believed that these experiences show that the problems in the management of psychotic tuberculous patients are not insurmountable.

Detection of Cases

The psychotic tuberculous patient probably represents a great source of infection and propagation of the disease, both in patient population and in their home communities. Bogen, Tietz and Grace (7) in 1934 surveyed the patients in Longview State Hospital, Cincinnati, Ohio. Their survey showed that tuberculous infection among mental hospital patients increases according to length of their stay in institutions and indicated that probably the majority of such patients contract their infection as well as their disease after their admission to the mental hospital. The present survey has revealed 28 patients who apparently

[1] From the Medical Service, Veterans Administration Hospital, North Little Rock, Arkansas.

[2] Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

contracted their infection in the hospital. The danger of spread of tuberculosis in home communities arises from: (*1*) discharge of patients on trial visit[3]; and (*2*) elopement of patients who have unrecognized active pulmonary tuberculosis. The present survey has revealed that 5 patients now under care were discharged in former years at a time when they probably had active pulmonary tuberculosis and thus undoubtedly were in a position to spread the disease.

How can these cases be discovered? The problem is difficult enough in mentally competent patients for it is well recognized that the tubercle bacillus may produce disease without early prominent symptomatology. It is even more difficult to detect the disease among psychotic patients. The latter often do not complain and many times when they do their complaints are quite bizarre. Too much dependence cannot be placed on physical signs for often the psychotic patient will not cooperate sufficiently to permit proper auscultation of the chest. Weight loss is a common finding in many psychotic patients and certainly it is not a specific sign of any one disease. Low grade fever may often be overlooked unless the temperature is taken at frequent intervals, a practice which is not usually a routine on most psychotic wards. This problem of detection of tuberculosis in psychotic patients has previously been well studied at the Ontario Mental Hospitals (Canada) (1). Reference will be made to these studies in the subsequent discussion.

Tuberculin testing is obviously not the answer. McGhie and Brink (8) tested 1,209 patients with tuberculin and 91.5 per cent had positive reaction whereas only 5 per cent had significant pulmonary lesions on roentgenography. The Ontario Mental Hospital group first used fever as a method of screening. The axillary temperatures of all patients were determined during one week out of every four months at 4 p.m. or 8 p.m. All patients with temperatures above 98° F. for four days or more were investigated for possible pulmonary tuberculosis. After the temperature observations, the erythrocyte sedimentation rates were determined for all patients; those with rates greater than 10 per cent in the first hour (Westergren Method) were investigated for possible pulmonary lesions. Roentgenographic screening was performed after temperature surveys had been conducted every four months for two years, and six months after a blood sedimentation rate survey. The roentgenographic examinations revealed that 2 per cent of the patients, unsuspected of disease on the basis of both temperature and blood sedimentation rate determinations, had lesions which were later proved to be active pulmonary tuberculosis. An additional 2.3 per cent of the patients had lesions the activity of which was questionable.

In July, 1946 there were 29 patients with active disease hospitalized on the tuberculosis ward at the Veterans Administration Hospital, North Little Rock, Arkansas. The patient population of the hospital at that time averaged between 1,600 and 1,800 patients. Roentgenographic surveys were begun. Since that time 76 patients with evidence of active pulmonary tuberculosis have been

[3] A probationary ninety day period during which time the patient is released in the custody of his nearest relative. If his adjustment is not satisfactory, he is returned to the hospital; otherwise, he is discharged and resumes his place in the community.

detected in the group hospitalized prior to July, 1946. In addition, 13 patients were found to have active pulmonary tuberculosis, previously unsuspected, on the basis of chest roentgenograms taken on admission. Moreover, since July, 1946, 5 attendants have been found to have the roentgenographic changes and laboratory findings of active pulmonary tuberculosis.

The use of 4 by 10 stereo photo-roentgen films is recommended in surveying cases. The detail of lung fields obtained compares favorably with that of the standard 14 by 17 chest films and the cost is much less. The present practice is to take a 4 by 10 stereo photo-roentgen film on each patient on admission to the hospital and at yearly intervals thereafter. Moreover, roentgenograms are obtained on all hospital personnel yearly with the exception of those who work on the tuberculosis ward who are examined at three month intervals. All suspicious lesions are checked by a standard 14 by 17 film. Patients with active pulmonary tuberculosis have a 14 by 17 film quarterly and those with arrested pulmonary tuberculosis have a 14 by 17 film every six months.

On the basis of the past two years' experience, the importance of these periodic roentgenographic and laboratory surveys can scarcely be overemphasized.

General Care of Patients

Isolation: The first essential in the care of tuberculous psychotic patients is segregation. Statistics as to the facilities for segregation in mental hospitals at the present time are not available. In 1927 such facilities were certainly inadequate. Klopp (9) in that year surveyed one hundred and six mental hospitals and found that only fifty-nine possessed detached pavilions for the isolation of tuberculous mentally ill patients.

The ideal arrangement consists of a separate building with a virtually autonomous service. Strict isolation procedures should be followed, *e g.*, the maintenance of clean and contaminated areas, the use of gowns, masks and caps, and routine hand scrubbing after contact with the patients. Rigorous cleanliness should prevail. The newer techniques of oiling floors and blankets, proved during recent years, should be utilized (10, 11). Preliminary treatment of laundry by the maintenance of temperatures of 220° F. for fifteen minutes should be performed in a laundry unit in the tuberculosis building. Food should be brought to the building in clean conveyors and transferred to conveyors that are not removed from the building. Proper supervision of disposal of waste garbage with incinerization, rather than supplementary feeding to animals, should be maintained. Surgical and roentgenographic facilities adequate to meet all needs should be present in the building. An occupational therapy unit and a recreation room should also be available.

The provision of such facilities need not require completely new construction. A regular ward building at the Veterans Administration Hospital at North Little Rock has been converted to furnish all of the above with the installation of only a small laundry, a surgical unit, and an X-ray room. Every effort has been expended to furnish adequate segregation as it is futile to expect psychotic patients to observe proper precautions when in contact with nontuberculous persons.

In each case treatment is outlined as would be prescribed for a mentally well person with tuberculosis of comparable severity. Treatment is then modified as dictated by the psychiatric condition.

Bed-rest: It is impossible to obtain as strict bed-rest as can be obtained in mentally competent patients, with one exception. The exception is provided by the patients whose illness has marked catatonic features. Nevertheless, a modified rest regimen is possible. If the patient is permitted to sit in a chair near his bed for a few specified hours per day, it often results in his accepting much more of a limitation of activity then he would observe with rigidly enforced bed-rest. In the majority of cases it has been possible to keep patients in bed for at least eighteen hours each day. This accomplishment is largely a result of the attitude of the nurses and attendants. Constant persuasion must be combined with friendliness and understanding. Restraint should never be used to try to maintain rest therapy though it sometimes becomes necessary in management of the patient's psychosis.

Once a routine of rest in bed with toilet privileges and specified hours of limited activity has been established, most of the newly admitted patients will follow this example to a surprising degree. In the presence of hyperactivity, moderate sedation should be added to the program. Phenobarbital in dosages varying from 0.03 Gm. to 0.09 Gm. three times daily has been very helpful.

The problem is best exemplified by the following case history of a difficult problem in management.

The patient, H. T., was a 24 year old white single male. In September, 1944 he became frankly psychotic and was hospitalized at the Veterans Hospital, North Little Rock, on October 5, 1944. A diagnosis of schizophrenic reaction, catatonic type, was made and he received twenty-five electric shock treatments. He showed some improvement and became able to care for himself but remained emotionally blunted, manneristic with signs of deterioration. Roentgenographic examination of the chest upon admission in October, 1944 revealed no evidence of tuberculosis. Chest roentgenogram in April, 1946 was reported as negative but in retrospect a small infiltration was present in the left lung. Roentgenogram of the chest in June, 1947 revealed an infiltration involving two-thirds of the left lung. Gastric lavage examination was positive for acid-fast bacilli on two occasions. A diagnosis of pulmonary tuberculosis, moderately advanced and active was made. Upon first being hospitalized on the tuberculosis service, the patient ate extremely poorly and was very hyperactive and refused to remain in bed. He did not resist being put to bed but refused to stay there. He continually asked to be put on an outside work detail. The attendants were instructed to check his bed frequently and to find the patient and put him back to bed whenever he was found to be up. He was told repeatedly why it was important that he remain in bed. He showed no real insight concerning this matter. An attendant was specially detailed to observe the patient during meal time and feed him, if necessary. He was given phenobarbital 0.09 Gm. three times daily. The sedation caused the patient to be less active. After approximately one month of constant attention, patient began observing bed-rest adequately. It was finally discovered that the patient could be induced to eat by refusing him coffee until he had eaten all of his meal. There was a spread of his disease to the opposite lung soon after he entered the tuberculosis service. However, a bilateral pneumothorax has been instituted successfully, and the patient now observes fairly good ward routine. His prognosis is believed to be good in regard to his pulmonary disease.

Although the above principles of therapy were formulated independently, it was later found that the conclusions were the same as those of the group at the Ontario Mental Hospital.

Nutrition: The problem of nutrition is the second problem of importance in each patient. The dietary regimen followed is the same as in the hospitals for the mentally competent. However, the coexistence of psychosis often interferes with adequate nutrition. The patient with a paranoid personality may harbor the delusion that the food is poisoned, the catatonic patient, in his retreat from reality, will cease to eat, and the hebephrenic patient may play with his food rather than eat it. Those who present eating problems must be picked out and given special attention. Every possible solution should be given a trial. The same attitude of constant persuasion combined with friendliness is essential. Some must be fed as a child is fed. Some will eat when fed by a woman but will refuse all food offered by a man. Only in a few paranoic patients and in those with the most severe catatonia does gastric lavage become necessary.

The following case represents a typical example of a feeding problem.

The patient was a 56 year old white male who was admitted to the Veterans Administration Hospital, North Little Rock, December 19, 1924. A diagnosis of schizophrenic reaction, catatonic type, was made. The patient has been a feeding problem throughout his period of hospitalization. He is apathetic, mute, negativistic and at times resistive. A progress note in 1930 notes the following: "The patient still will eat for only one attendant and when that attendant is off duty, refuses to eat. He will take exercise only under the supervision of that one attendant." The patient was given eight electric shock treatments in 1946 but this did not improve his condition.

Roentgenographic examinations of the patient's chest were negative until 1946. In August, 1946 he was noted to have developed infiltration and cavitation in the left lung. Four sputum examinations were positive for acid-fast bacilli. The patient's psychiatric condition is such that he is not a candidate for major thoracic surgery. Minor collapse measures have failed. During his period of hospitalization on the tuberculosis service he has continued to present a problem in nutrition. At intervals he refuses to eat altogether. After being tube fed for periods varying from one to five weeks, he will suddenly resume eating voluntarily. He consistently refuses to eat from a tray but will eat in the dining hall at times. He eats better when fed by a woman than by a man. He often will take liquid nourishment and steadfastly refuse solid food.

Laboratory Investigations: The problem of laboratory investigation of the etiology and activity of the pulmonary lesions is also in need of special attention. Isolation of *M. tuberculosis* is necessary to establish the diagnosis. This presents many problems not encountered in the mentally competent patient. Sputum specimens are often difficult and sometimes impossible to obtain. Methods must be utilized to prevent one patient from using another's sputum cup. If all efforts to obtain sputum specimens from a patient are unsuccessful, gastric lavage must be performed. The initial use of this procedure often necessitates active restraint of the patient. It is significant, however, that most psychotic patients soon learn to undergo lavage without objection. The lavage specimens may be examined by direct smear but positive reports should be verified by culture or animal inoculation.

Roentgenographic evidence of cavitation and progression or regression of pulmonary infiltration in serial films is unquestionable proof of activity. However, lack of change does not necessarily mean that a particular lesion is arrested. Moreover, the etiology of a pulmonary lesion cannot be definitely established merely by its appearance on a roentgenogram.

Additional measures, such as an elevated erythrocyte sedimentation rate or monocytosis, as opposed to lymphocytosis, in the peripheral blood, are suggestive of activity but are nonspecific. The same is true of such clinical findings as fever and weight loss. A negative skin tuberculin reaction is believed to be strong evidence against the presence of tuberculosis in all except miliary or terminal pulmonary infections.

Laboratory investigations have been stressed because this problem often seems insurmountable to physicians unaccustomed to working with psychotic patients. The importance of the problem of differentiating arrested and active lesions is self-evident. In the writers' opinion, the conservative attitude of the group working at the Ontario Mental Hospital is to be commended. They recommended that patients who had once had proved active pulmonary tuberculosis should have negative sputum examinations for tubercle bacilli, normal erythrocyte sedimentation rates, and stationary lesions, as determined by serial roentgenography, for one year before being returned to contact with nontuberculous patients. During the latter six months of this period, the patient should be allowed full exercise and light work, if his mental condition permits. The Canadian investigators believed that it is extremely doubtful whether patients with moderately advanced or far advanced pulmonary tuberculosis should ever be returned to contact with nontuberculous patients because of the great possibility of relapse accompanied by a return of infectiousness. Burns (12) reiterates this philosophy when he states, "In our cases, those becoming chronic with stationary stabilized infiltrations tend to become more and more self-limited and, with the increasing age of the lesion, of little danger to the future well-being of the host. Only as they remain carriers of the tubercle bacilli do they play an important part in our tuberculosis control program."

Active Therapy

Thoracoplasty, pneumothorax, pneumoperitoneum, and phrenico-exeresis have all been utilized in the treatment of the patients in the present series. Closed intrapleural pneumonolysis has been employed when indicated. The criteria for the selection of cases for collapse therapy, in reference to the type and status of the patient's pulmonary lesion, are the same as those used in mentally competent patients. The early institution of collapse therapy is favored, however, because: (*a*) many psychotic patients are unable to follow the bed-rest schedule and it is felt that such patients should be given the benefit of collapse therapy at an early date; (*b*) those psychotic patients who will follow a bed-rest schedule, such as those with well developed catatonic features, are just the ones whose mental condition would be benefitted by encouraging them to indulge in more activity. Thus, the sooner their pulmonary lesion is in a state to allow activity

the quicker the more active measures can be taken in treating their neuropsychiatric condition.

The psychiatric status must also be taken into consideration in each individual case. In general, it is felt that collapse therapy, including major thoracic surgery, is indicated in those patients whose outlook for a remission of their mental disease and ultimate discharge is reasonable. Also those patients who probably will not be able to leave the hospital but can adjust to minimum supervision and maximum privileges should be given serious consideration.

It is not believed that extensive surgical procedures are indicated in the chronic deteriorated psychotic patient whose psychiatric prognosis is hopeless and who must spend the remainder of his life under close supervision. However, minor surgical procedures, such as pneumothorax, pneumoperitoneum, and phrenico-exeresis have been employed in this group of patients without difficulty.

The active participation of the psychiatrist in the selection of cases for collapse therapy is an absolute necessity. This is particularly true for those patients who are candidates for major thoracic surgery.

In the actively psychotic patient with active pulmonary tuberculosis the decision must be made as to which illness to treat with the greater emphasis. The disturbed, hyperactive patient cannot be made to observe bed-rest to any degree. He also is unable to cooperate adequately with specific forms of treatment, and is difficult to manage during the postoperative period, if surgery is undertaken. This was well illustrated by one patient in the present series who expired following a second stage thoracoplasty. A brief summary of this case follows.

C. E. H., age 52, was admitted to this hospital March 27, 1946. The history revealed that the patient had been a chronic alcoholic for most of his adult life and in 1944 he was admitted to a state hospital in California following a long period of drinking. A diagnosis of psychosis, alcoholism, alcoholic neuritis and Korsakoff's syndrome was made. The patient failed to show improvement and was transferred to this hospital. On admission he was completely disoriented and showed marked impairment of memory for both recent and remote events. He later developed delusional ideas and was continually hyperactive, requiring frequent sedation and mechanical restraints. No improvement in his mental condition was noted during his hospitalization and on June 12, 1947 his diagnosis was changed to psychosis, alcoholic deterioration. Roentgenographic examination of the chest on admission to the hospital showed pulmonary infiltration in the right apex and first interspace. No cavities were seen. Gastric lavages were positive for the presence of acid-fast bacilli. Pneumothorax on the right was instituted February 3, 1947. Roentgenogram of the chest following institution of pneumothorax revealed the presence of pleural adhesions and a closed intrapleural pneumonolysis was attempted on March 25, 1947, but was unsuccessful. Thoracoplasty on the right was recommended and the first stage was performed on May 28, 1947 and the first three ribs were resected. The anesthesia used was nitrous oxide and oxygen and sodium pentothal intravenously. The patient's postoperative course was uneventful except for the difficulties experienced as a result of his mental condition. He seemed completely unaware that he had had an operation. He insisted on being out of bed immediately and used his arm on the operated side without apparent pain or discomfort. He demanded and consumed large quantities of food. Immediately postoperatively considerable sedation was required in order to control the patient. On the 25th of June, 1947 second stage thoracoplasty was performed and the fourth, fifth, sixth, and seventh ribs were resected. The

patient's immediate postoperative condition was good. On the first postoperative day he developed considerable abdominal distension accompanied by respiratory difficulty. Improvement was noted after tap water enemas and injection of prostigmine and the use of an oxygen tent. On the second postoperative day his condition was much improved and the oxygen was discontinued. At 6:25 p.m. on the second postoperative day patient sat on the side of bed and drank some coffee. After a few minutes he suddenly fell back on the bed, gasped, and respirations were observed to have ceased. Although postmortem examination was not performed and the exact cause of death remains obscure, it is believed that the patient's hyperactivity and general psychiatric status interfered in the proper management of his care.

It is now believed that an attempt should be made to improve the psychiatric condition of such patients before attempting major surgery. Shock therapy or prefrontal leukotomy would appear to offer the greatest possibility for a remission in the patient's psychosis.

In the past, pulmonary tuberculosis, active or arrested, has been generally considered a contraindication to shock therapy. More recently, however, a more liberal attitude has been adopted by some people. Moore (13) states that when proper precautions are followed and where the need is sufficient, latent, arrested, or even active pulmonary tuberculosis does not constitute an absolute contraindication to shock therapy.

The opinion expressed by Wilcox (14) in regard to the contraindications to shock therapy in general is felt to be worthy of emphasis and is quoted here: "The contraindications to shock therapy are related to the complications which may occur but are modified by the skill of the physician in preventing the complications and by the relative importance attached to the complications. Obviously, the more severe the mental illness the greater the risks that will be tolerated in the hope of therapeutic gain, but as the therapy is applied to milder cases the possible complications must be weighed even more carefully."

Certainly in many psychotic patients with pulmonary tuberculosis, the psychosis is more of a detriment to recovery than would be the case with shock therapy.

Reports of cases with pulmonary tuberculosis that have been given shock therapy are meager. Bulley and Greene (15) report one patient with an acute recent psychosis and active tuberculosis who was given metrazol shock, with improvement and subsequent arrest of the tuberculosis.

At the present time two patients on the writers' service are receiving electric shock therapy with curare. One of these patients has arrested minimal tuberculosis, and the other has a moderately advanced lesion that is active but has been stable for six months. Both patients have been under treatment for too short a time for any conclusions to be drawn as to the effect of electric shock therapy on the pulmonary lesions.

In the hands of an experienced neurosurgeon prefrontal leukotomy does not constitute a serious threat to the patient even if active pulmonary tuberculosis is present. One patient with far advanced pulmonary tuberculosis, who had been psychotic for many years, had a prefrontal leukotomy, following which a a two stage thoracoplasty was performed in conjunction with streptomycin

therapy. His progress thus far has been satisfactory, and his outlook for recovery definitely improved. It is believed that the surgical therapy of the tuberculosis would not have been possible without the preceding prefrontal leukotomy. A brief case summary follows:

P. L. H., age 57, was admitted to this hospital on December 13, 1945. The patient had shown evidence of severe mental illness for many years and had been diagnosed as schizophrenic reaction of the hebephrenic type. A roentgenographic examination of the chest revealed the presence of a minimal infiltration in the right lung. The left lung showed a chronic proliferative inflammatory process extending from the second to the seventh ribs anteriorly. A cavity appeared to be present in the left second interspace. No active therapy was undertaken at this time. Reexamination in February, 1947 again revealed the previously reported pulmonary infiltration. There appeared to have been very slight regression since December, 1945. Investigations were carried out to determine the etiology of the pulmonary lesion demonstrated on the roentgenogram. The erythrocyte sedimentation rate was found to be 32 mm. per hour. The patient was unable to cooperate in producing sputum specimens and gastric lavage could only be performed by restraining the patient. The few lavage specimens obtained at this time were reported as negative for tubercle bacilli. The patient's mental disease was characterized by many bizarre delusions in reference to the genito-urinary and gastro-intestinal tracts. He also had many delusions of a religious nature. These abnormal thought processes were so disturbing that the patient required very close supervision and sedation. He refused to allow the windows to be opened near his bed, objected to any light in the room, and demanded that the other patients leave the radio off at all times. He was so insistent in these demands that he was involved in frequent fights with other patients. In view of the severity and long-standing nature of the patient's mental illness and the presence of undoubtedly active pulmonary tuberculosis, the patient's case was reviewed by the medical and psychiatric Staff. On their recommendation, a prefrontal leukotomy was performed on June 18, 1947. Postoperatively a marked improvement in his attitude and behavior was noted. He was cheerful, became interested in the ward activities, and cooperated fairly well with bed-rest and diagnostic procedures. More gastric lavages were performed and were reported as positive for the presence of acid-fast bacilli, thus establishing the diagnosis of active pulmonary tuberculosis. The patient's mental improvement continued and was felt to be such that a trial visit could be anticipated if his pulmonary tuberculosis could be brought under control. With this in view, pneumothorax on the left was initiated on August 5, 1947. It was discontinued, however, on August 19, 1947, because of the presence of pleural adhesions that were unsuitable for pneumonolysis. The patient's case was then reviewed by the Assistant Branch Chief of Tuberculosis and a thoracoplasty on the left was recommended. Streptomycin was to be given in conjunction with the thoracic surgery. The patient was started on streptomycin December 15, 1947, 0.5 Gm. twice a day. The first stage thoracoplasty was performed on February 11, 1948 and the first three ribs were resected. The anesthesia consisted of intravenous sodium pentothal, nitrous oxide and oxygen and curare. The patient withstood the procedure well and the postoperative period was free of complications. The second stage thoracoplasty was performed on March 10, 1948 and the fourth, fifth, sixth, and seventh ribs were resected. Again the patient withstood the procedure well and the immediate postoperative period was free from complications. At the present time the patient has shown some exacerbation of his mental disease. His attitude is one of antagonism and quarrelsomeness. It is felt, however, that, as his general physical condition improves and his feeling of well-being returns, his mental condition will again show improvement. Roentgenographic examination of the chest shows an adequate collapse of the diseased portion of the left lung. The minimal infiltration noted in the right lung on admission has remained stable. It is believed that this case shows that one can salvage at least a small percentage of patients with a disturbing psychosis and pulmonary tuberculosis.

Although this patient's case is not closed at the present, it is believed that his outlook has been definitely improved.

The institution of psychiatric treatment of the sort discussed above is not always necessary before starting such collapse measures as pneumothorax, pneumoperitoneum or phrenic nerve operations. In none of the 33 patients in whom pneumothorax has been started has it been necessary to discontinue the treatment because of the psychiatric condition. Altshuler and Bailey (16) also report that, of 100 patients treated with pneumothorax, only one was unable to continue to receive the treatment because of uncooperativeness.

In the cases suitable for pneumothorax, it is advisable first to establish the pneumothorax if possible and then to proceed with specific therapy for the mental disease, such as shock therapy or prefrontal leukotomy. The period of time necessary before proceeding with shock or prefrontal leukotomy varies with the individual case. In the disturbed hyperactive patient, measures should be taken as soon as possible in order to improve the patient to the point that he can at least accept a modified bed-rest regimen. On the other hand, it would probably be justified to wait until the patient's pulmonary tuberculosis is partially controlled in those patients who are quiet and fairly cooperative (catatonic, depressed). It should be remembered that the per cent of remissions following all forms of shock therapy decreases rapidly as the duration of the psychosis increases.

The writers present the following outline of a program for the care of the psychotic patient with pulmonary tuberculosis. It is realized that the presentation of such a program carries the risk of over simplification of the problem since each case must be considered individually.

The patients are divided into three large groups: A, B and C.

Group A patients include those whose psychosis is of recent origin and is of a type which may be expected to improve with specific therapy. If evaluation of the patient's pulmonary lesion indicates that collapse therapy should be undertaken, two courses of action are considered. In the disturbed hyperactive and uncooperative patients in which suitable collapse therapy cannot be instituted because of the patient's mental condition, it is advisable to proceed with specific therapy directed to alleviate the mental illness (*i.e.*, shock therapy, prefrontal leukotomy, or antisyphilitic therapy). Collapse therapy is then instituted as soon as the patient's mental condition is such that he can cooperate to a sufficient degree.

In the less disturbed, more cooperative patients in whom collapse therapy is indicated, it can be started first and then followed at a later date by specific treatment of the mental disease.

Group B patients are those whose psychosis is of a chronic nature and of such a severity that they are unable to leave the hospital but can adjust to minimum supervision. Many of these patients may be considered mentally competent as far as their cooperation in any treatment program is concerned. Depending upon the individual patient, collapse therapy is carried out in the same way as with a similar group of mentally competent patients.

Group C patients include those who have a psychosis of a chronic nature and who are either chronically disturbed or show marked mental regression and deterioration. It is this group of patients in which the highest incidence of pulmonary tuberculosis is found. Although it may be possible to carry out collapse therapy in a few of these patients, it is the exception rather than the rule. In general, no specific treatment is indicated except segregation from the hospital population. It is, however, in this group that prefrontal leukotomy should always be considered.

Thoracoplasty

The first thoracoplasty was performed at this institution in November, 1946. Since that time the procedure has been completed in 11 patients. Detailed information concerning these patients is presented in table 1. The youngest patient was 25 and the oldest 58 and the average age for the group was 47 years. Seven of the 11 patients had a trial of pneumothorax prior to thoracoplasty. In all 11 patients, pneumothorax was discontinued because of the presence of pleural adhesions unsuitable for pneumonolysis. The patients selected for thoracoplasty, with few exceptions, were those whose psychiatric prognosis was fairly good or those who had been able to make a satisfactory hospital adjustment (*i.e.*, open ward).

The operations were all performed by the local Consultant in Thoracic Surgery. The anesthesia has been of two types, local and general. The patients operated under local (1 per cent novocaine) received luminal 0.3 Gm., morphine .010 or .015 Gm. and hyoscine .0006 Gm. as a basal anesthetic. Five patients were operated upon under local anesthesia but only patients that were of fair mental competence or had marked catatonic features were selected for this type of anesthesia. All of the patients who received only local anesthesia were managed with difficulty during the operations.

General anesthesia was used in the remaining 6 patients, and consisted of intravenous sodium pentothal, nitrous oxide and oxygen and curare, with endotracheal intubation. All uncooperative disturbed cases were done under general as described.

There were two postoperative deaths in the group. The clinical course of one, C.H., was summarized above. The other, J.E.E., died on the third postoperative day. Postmortem examination revealed thrombosis of the superior sagital sinus and its main tributaries, with multiple hemorrhagic infarcts of the brain.

Although sufficient time has not elapsed for final disposition of the 9 surviving patients, 3 are being considered for trial visit, 4 are to be transferred to a ward allowing them to lead a more normal life, one has been recommended for prefrontal leukotomy, and the psychiatric status of one patient is such that continued close supervision will be necessary.

Pneumothorax

As previously noted, some physicians have been extremely pessimistic in regard to the use of pneumothorax in psychotic patients. Thirty-three of the

TABLE 1

Thoracoplasty cases

NAME	AGE	EXTENT OF PULMONARY DISEASE	NEUROPSYCHIATRIC DIAGNOSIS AND STATUS	DATE THORACOPLASTY COMPLETED	ANAESTHESIA	COMPLICATIONS	DISPOSITION
C. E. H.	52	M. A.	Psychosis, alcoholic deterioration, chronically disturbed, hyperactive. Requiring restraint and sedation.	Second stage 6-25-47	General	Died on second postoperative day.	
P. L. H.	57	F. A.	Schizophrenic reaction, hebephrenic type. Chronically disturbed, hyperactive. Requiring sedation and occasionally restraint. Prefrontal leukotomy performed prior to thoracoplasty with good result.	Second stage 3-10-48	General	Feeding problem. Requiring prolonged parenteral medication	Trial visit contemplated at the end of postoperative period of observation.
W. A. S.	55	M. A.	Paresis, in partial remission. Well adjusted hospital patient.	Second stage 2-12-47	Basal and local	None	Discharge by transfer to Old Soldiers' Home.
O. D. M.	29	M. A.	Schizophrenic reaction, hebephrenic type. Seclusive, paranoid, occasionally hyperactive and a feeding problem.	Second stage 4-10-47	Basal and local	Continued to be a feeding problem during postoperative period. Tube feeding required.	Except for poor food intake, patient showed improvement in mental condition. Trial visit contemplated.
J. V. S.	25	MIN	Schizophrenic reaction, hebephrenic type. Seclusive, regressed, manneristic, occasionally hyperactive.	Second stage 12-17-47	General	None	No change in mental condition. Continued hospitalization necessary. To be transferred to another ward when postoperative observation complete.

F. R. R.	47	M. A.	Schizophrenic reaction, hebephrenic type. Seclusive but a well adjusted hospital patient.	Second stage 2-17-48	General	None	Trial visit contemplated at the end of postoperative period of observation.
J. E. E.	58	M. A.	Schizophrenic reaction, hebephrenic type. Seclusive and delusional.	First stage 7-23-47	General	Died on second postoperative day.	
A. C.	51	M. A.	Paresis, delusional, hypochondriacal.	Second stage 8-13-47	Basal and local	None	Increased privileges. Trial visit contemplated.
A. L. W.	53	M. A.	Schizophrenic reaction, paranoid type. Depressed, seclusive, delusional.	Second stage 4-11-47	Basal and local	None	Prefrontal leukotomy planned.
E. C. K.	52	M. A.	Schizophrenic reaction, hebephrenic type. Regressed, delusional, feeding problem.	Second stage 4- 7-48	General	Feeding problem. Spread of lesion after first stage. Patient given streptomycin before proceeding with second stage.	Mental condition requires continued hospitalization under close supervision.
R. S. I.	52	M. A.	Schizophrenic reaction, hebephrenic type. Paranoid and seclusive.	Second stage 1-29-47	Basal and local	None	Open ward privileges.

patients in the present series have been given a trial of pneumothorax without undue difficulty. No sedative therapy was considered to have been necessary in these patients. It is recognized, however, that in some patients sedative therapy would be indicated. It is believed that pneumothorax cannot be given to certain patients, such as the extreme paranoid or agitated manic patient, but these will be the exception rather than the general rule. Moreover, if collapse therapy is indicated in such a patient, the possibility of performing prefrontal leukotomy or electric shock treatment before the collapse therapy should be considered in order to give better cooperation.

Summarization of table 2 indicates the following. An attempt was made to establish thirty-seven pneumothoraces. Five pneumothoraces were successfully instituted without pneumonolysis and eleven were successfully instituted with the aid of intrapleural pneumonolysis. Two bilateral pneumothoraces were started and maintained. Twenty-one pneumothoraces were unsuccessful because of adhesions that prevented therapeutic collapse and were not amenable to intrapleural pneumonolysis. There have been no complications in the group which did not require pneumonolysis. Only one complication was encountered in the unsuccessful group. Six complications occurred in the group requiring intrapleural pneumonolysis: adhesive pleuritis, 1; pleural effusion, 3; spread of disease, 1; and traumatic pneumothorax with massive collapse and death, 1. Four of the patients in this group of 33 have died. The death of only one was related to pneumothorax therapy.

It is recognized that these results are not as favorable as some published series; nevertheless, the failure to achieve better results cannot be attributed to the patients' psychoses. The failure to achieve better results is principally a consequence of the long duration of disease prior to the attempts at collapse therapy.

The patients' psychoses have not constituted a serious problem in management even in regard to intrapleural pneumonolysis. This surgical procedure can be successfully performed, even in the agitated patient, by use of general anesthesia with sodium pentothal. Cooperation during the postoperative period can be obtained by means of sedation and special nursing care. The "special" nurse is a factor of great importance in the postoperative course of any psychotic patient. Constant observation, untiring patience, persuasive charm, and knowledge of the importance of the compliance with postoperative orders are requisite in every "special" nurse.

It is the opinion of some that pneumothorax is not a worthwhile procedure in older age groups. Attention should be drawn to the fact that it was possible to institute pneumothorax successfully in 12 patients 45 years of age or older. From this limited experience it is believed that collapse can be successfully instituted in older age groups far more often than is generally realized. It is impossible to predict success or failure accurately and the attempt at collapse therapy should be made if the patient is considered a suitable candidate for pneumothorax.

One final fact can be demonstrated by analysis of this group. Seventeen of

the 33 patients contracted pulmonary tuberculosis after entering this hospital. This demonstrates the striking need for better control of tuberculosis in mental hospitals.

Other Collapse Measures

Phrenico-exeresis and pneumoperitoneum have also been found applicable in psychotic patients. The former procedure has been performed in 5 patients. Phrenico-exeresis has been reserved for situations in which it is desired to give the diseased lung additional protection against reactivation or extension of disease. The results have been equivocal.

Pneumoperitoneum has been instituted in two patients without difficulty. The concept has been followed that this form of therapy is indicated in patients with bilateral disease whose lesions are predominantly exudative in character. Pneumoperitoneum may also be used in certain selected patients who would be candidates for major chest surgery except for their psychiatric status. The following case history is cited to demonstrate such a patient.

J. A.S., age 53, was admitted to this hospital September 4, 1938. A diagnosis of psychosis, syphilitic meningo-encephalitic type, was made on admission. The syphilologist believed that no further antisyphilitic therapy was indicated. The patient showed marked mental regression and deterioration. He was unable to carry on a normal conversation and his psychiatric prognosis seemed hopeless. First evidence of pulmonary tuberculosis was discovered on routine roentgenogram of the chest in November, 1945. At that time an area of pulmonary infiltration was observed in the right apex and first interspace. Since 1945 there has been a moderate increase in the extent of the lesion but no spread to the contralateral lung. Gastric lavages have been positive for the presence of acid-fast bacilli. Right pneumothorax was initiated in March, 1947. Collapse was inadequate because of multiple adhesions which did not appear to be amenable to pneumonolysis. Therefore, pneumothorax was discontinued. The patient's psychiatric condition was so bad and his physical condition was so poor that thoracoplasty was thought to be contraindicated. He was tube-fed from July, 1947 through October, 1947 and his general physical condition improved. Pneumoperitoneum was begun in September, 1947. Recent roentgenographic examination of the chest revealed definite decrease in the extent of the infiltration in the lung. Phrenico-exeresis on the right is being considered at the present time to increase the elevation of the right diaphragm.

SUMMARY

The purpose of this paper has been to show that problems in the management of psychotic patients with pulmonary tuberculosis are not insurmountable. The fact that an appreciable number of psychotics make at least a partial recovery and return to their families and home communities and the problem of control of the disease in the institution make a more active approach desirable.

Conclusions based on experience with over 100 psychotic patients with tuberculosis are reported. Routine roentgenographic survey of the patient population has been proved to be the best method of detection of cases. General management of these patients has been discussed in detail with special emphasis on the problems of rest, nutrition, and collapse therapy. All forms of collapse therapy can be successfully carried out in selected psychotic patients. In

TABLE 2

Pneumothorax cases

NAME	KNOWN DURATION DISEASE	EXTENT OF DISEASE	AGE	PNEUMOTHORAX SUCCESSFUL WITHOUT AID	PNEUMOTHORAX SUCCESSFUL WITH PNEUMONOLYSIS	PNEUMOTHORAX UNSUCCESSFUL (ADHESIONS)	COMPLICATIONS	NEUROPSYCHIATRIC DIAGNOSIS AND STATUS
	yrs.							
N. S. A.	4	Min. unilateral	56			Yes	None	Schizophrenic reaction, catatonic type. Depressed, seclusive.
A. S. C.	11	MA bilateral (left, obsolete fibrosis)	48	(a) right, yes			None	Schizophrenic reaction, paranoid type. Delusional, occasionally disturbed and hyperactive.
A. C.	2	MA unilateral	51			Yes	None	Psychosis, syphilis, meningoencephalitic type. Delusional, hypochondriacal.
A. D.	4	MA unilateral	46			Yes	None	Schizophrenic reaction, simple type. Hypochondriacal, occasionally disturbed.
A. G.	1½	MA bilateral	57		(a) right, yes	(a) left, yes	None None	Psychosis, epileptic deterioration. Paranoid, argumentative, occasionally combative.
J. G.	2	MA unilateral	28		Yes		Adhesive pleuritis. Pneumothorax discontinued.	Schizophrenic reaction, catatonic type. Seclusive, manneristic.
W. L. H.	5	Min unilateral	51			Yes	None	Schizophrenic reaction, hebephrenic type. Deteriorated, manneristic, occasionally hyperactive.

F. C. H.	4	MA bilateral	55		(a) right, yes		Pleural effusion. Pneumothorax continued; effusion controlled by thoracentesis.	Schizophrenic reaction, hebephrenic type. Deteriorated, manneristic, compulsive.
J. K.	29	MA unilateral	56			Yes	None	Schizophrenic reaction, catatonic type. Seclusive, mute.
E. J. K.	3	MA unilateral	57	Yes			None	Psychosis, syphilis, meningo-encephalitic type. Seclusive, delusional.
W. C. K.	10	MA bilateral	60	(a) right, yes (a) left, yes			None None	Schizophrenic reaction, hebephrenic type. Seclusive, delusional.
W. H. L.	2	FA bilateral	51		(a) left, yes		Pleural effusion with pocketing. Pneumothorax discontinued.	Schizophrenic reaction, hebephrenic type. Deteriorated, delusional, occasionally hyperactive.
O. D. M.	2	MA unilateral	28			Yes	None	Schizophrenic reaction, hebephrenic type. Seclusive, paranoid, occasionally hyperactive and a feeding problem.
R. H. M.	14	Min unilateral	48			Yes	None	Schizophrenic reaction, hebephrenic type. Seclusive, deteriorated.
L. R. M.	2	MA unilateral	57		Yes		None	Schizophrenic reaction, hebephrenic type. Delusional.
U. L. N.	9	MA unilateral	50			Yes	None	Psychosis, syphilis, meningoencephalitic type. Delusional.

TABLE 2—*Continued*

NAME	KNOWN DURATION DISEASE	EXTENT OF DISEASE	AGE	PNEUMOTHORAX SUCCESSFUL WITHOUT AID	PNEUMOTHORAX SUCCESSFUL WITH PNEUMONOLYSIS	PNEUMOTHORAX UNSUCCESSFUL (ADHESIONS)	COMPLICATIONS	NEUROPSYCHIATRIC DIAGNOSIS AND STATUS
	yrs.							
J. D. P.	2	MA bilateral (left, obsolete fibrosis)	53			(a) right, yes	None	Schizophrenic reaction, hebephrenic type. Effect not appropriate.
F. R. R.	17	MA bilateral (left, obsolete fibrosis)	47			(a) right, yes	None	Schizophrenic reaction, hebephrenic type. Seclusive but a well adjusted hospital patient.
J. H. S.	2	MA unilateral	52			Yes	None	Psychosis, syphilis, meningoencephalitic type. Deteriorated, regressed, feeding problem.
J. V. S.	2	Min unilateral	24			Yes	None	Schizophrenic reaction, mixed type. Seclusive, regressed, manneristic, occasionally hyperactive.
J. E. S.	5	MA bilateral (left, stable)	45	(a) right, yes			None	Schizophrenic reaction, hebephrenic type. Delusional, some deterioration.
S. S.	6	MA unilateral	59			Yes	None	Psychosis with mental deficiency.

J. S.	2	MA bilateral (right, stable)	53		(a) left, yes		None	Schizophrenic reaction, hebephrenic type. Delusional and excitable.
H. N. T.	1	MA bilateral	24		(a) left, yes (b) right, yes		Spread to right lung necessitating right pneumothorax.	Schizophrenic reaction, hebephrenic type. Deteriorated, hyperactive.
B. B.	9	Min unilateral	54		Yes		Pleural effusion.	Schizophrenic reaction, hebephrenic type. Deteriorated, hyperactive, regressed.
G. B.	13	FA bilateral (confined to upper lobes)	55		(a) right, yes	(a) left, yes	Patient expired following traumatic pneumothorax with massive collapse in presence of bilateral pneumothorax.	Schizophrenic reaction, hebephrenic type. Deteriorated, manneristic, regressed.
A. C.	15	MA unilateral	63			Yes	None	Psychosis, syphilis, meningo-encephalitic type. Seclusive, paranoid, resistive to therapy.
A. C. G.	2	MA unilateral	56			Yes	Tension pneumothorax with bronchopleural fistula and development of empyema.	Schizophrenic reaction, catatonic type. Seclusive, mute, occasionally agitated, a feeding problem.
P. L. H.	2	FA bilateral (right, healed min. lesion)	57			(a) left, yes	None	Schizophrenic reaction, hebephrenic type. Chronically disturbed and hyperactive, requiring sedation and occasional restraint.

TABLE 2—*Concluded,*

NAME	KNOWN DURATION DISEATE	EXTENT OF DISEASE	AGE	PENUMOTHORAX SUCCESSFUL WITHOUT AID	PNEUMOTHORAX SUCCESSFUL WITH PNEUMONOLYSIS	PNEUMOTHORAX UNSUCCESSFUL (ADHESIONS)	COMPLICATIONS	NEUROPSYCHIATRIC DIAGNOSIS AND STATUS
	yrs.							
C. H.	1	MA uni-lateral	53			Yes	None	Psychosis, alcoholic deterioration, chronically disturbed and hyperactive, requiring restraint and sedation.
E. C. K.	11	MA uni-lateral	52			Yes	None	Schizophrenic reaction, hebephrenic type. Regressed, delusional, feeding problem.
L. L.	3	FA uni-lateral	54			Yes	None	Psychosis, syphilis, meningo-encephalitic type. Deteriorated, hyperactive.
F. G. M.	13	Min. uni-lateral	56		Yes		None	Psychosis, syphilis, meningo-encephalitic type. Some deterioration.

general, however, major thoracic surgery should be reserved for those patients with a favorable prognosis for remission of their psychoses or the ones who have made a satisfactory adjustment under maximum privileges and minimum supervision. Shock therapy and prefrontal leukotomy in an effort to improve the mental status are applicable in certain selected cases of psychotic tuberculous patients.

SUMARIO

La Asistencia de la Tuberculosis en los Psicóticos

Tiene por propósito este trabajo demostrar que no son insuperables los problemas planteados por los psicóticos que padecen de tuberculosis pulmonar. El hecho de que una proporción apreciable de los psicóticos se reponen por lo menos parcialmente y regresan a sus hogares y colectividades y el problema creado por la lucha contra la enfermedad en una institucion indican la conveniencia de un ataque más activo.

Las conclusiones presentadas básanse en las observaciones realizadas en más de 100 psicópatas con tuberculosis. Las encuestas radiográficas sistemáticas de los enfermos del establecimiento ha resultado ser el método mejor para el descubrimiento de casos. Discutese a fondo la asistencia general de esos sujetos, recalcando en particular los temas del descanso, la nutrición y la colapsoterapia. En los psicóticos seleccionados pueden ejecutarse con éxito todas las formas de la colapsoterapia; pero, en general, debe reservarse la cirugía torácica mayor para aquellos en los que el pronóstico para la remisión de la psicosis es favorable o que han logrado un ajuste satisfactoria con un máximo de libertad y un mínimo de vigilancia. En ciertos tuberculos psicóticos bien escogidos tienen su aplicación el choc terapéutico y la leucotomía prefrontal con mira a mejorar el estado mental.

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ON FULMINANT TUBERCULOUS SEPTICEMIA WITH LEUKOPENIA

WALTER PAGEL AND A. L. WOOLF[1]

INTRODUCTION

The term, fulminant tuberculous septicemia, is used to describe a rapid process of generalised tuberculosis which either fails to cause any grossly detectable lesions or produces multiple necrotic areas which do not resemble the classical structure of tuberculous foci, but are replete with tubercle bacilli. Only 11 such cases have been described in the literature and most of them showed evidence of primary abdominal infection associated with a characteristic leukopenia (1). The diagnosis of tuberculous septicemia in all of these cases is made from the fulminant clinical picture often resembling typhoid fever, in concert with the anatomical changes, rather than by the demonstration of tubercle bacilli in the circulating blood. The latter is still subject to technical difficulties and a positive result may be obtained in the terminal stages of pulmonary phthisis, without the presence of fulminating tuberculous septicemia.

In this hospital, 2 cases of fulminant tuberculous septicemia have been observed. One of these cases presented evidence of primary abdominal infection and belonged to the second category, *i.e.*, producing grossly detectable necrotic foci (1). The second case, to be reported below, is of special interest in that it originated in a straightforward primary pulmonary infection and belonged to the first category of cases without macroscopic lesions.

CASE REPORT

Clinical illness: The patient was a 56 year old man who had felt well until one month before admission, at which time he had fainted and fallen in the street. Improvement was slow and anorexia, disinterest, increasing deafness, and rash on face, arms and legs persisted. Five days before admission the patient was noted to have twitching of face.

Physical examination on admission to the hospital revealed a temperature of 101°F., a respiratory rate of 40 per minute and diffuse coarse rhonci over both chests. The total leukocyte count was 2,050 per cu. mm., of which 46 per cent were neutrophils. A chest roentgenogram revealed the shadows of a patchy consolidation and partial collapse of the right lower lobe. The clinical diagnosis was agranulocytosis and auricular flutter. The possibility that the patient also had psittacosis was considered.

The course of the illness was one of progressive physical and mental deterioration. The auricular flutter was converted to auricular fibrillation with a rapid ventricular rate. Crepitations were detected at the lung bases. The total leukocyte count fell to 250 per cu. mm. and the blood urea nitrogen was 73 mg. per 100 cc. The lungs became increasingly congested and slight anomalous ocular signs with inequality of pupils appeared just before death. The cell count of the cerebrospinal fluid increased from one to 156 per cu. mm. The patient died eight days after admission to the hospital.

Postmortem findings: Both lower lobes of the lungs were consolidated and hemorrhagic, with the process being more pronounced on the right. The other lobes were congested.

[1] From the Central Middlesex County Hospital, London, N. W. 10, England.

A subpleural wedge-shaped caseous area 2 by 1 cm. was found in the anterior axillary aspect of the right lower lobe (figure 1). The lymph nodes at the bifurcation of the trachea were very enlarged (7 by 5 cm.) and formed a solid hard white mass (figure 2). The paratracheal nodes were also enlarged. The liver weighed 1,520 Gm. and was pale. The spleen was dark and soft and contained a partly hemorrhagic infarct, 2.5 cm. in diameter, near the upper pole. The infarct was demarcated by a narrow yellowish white

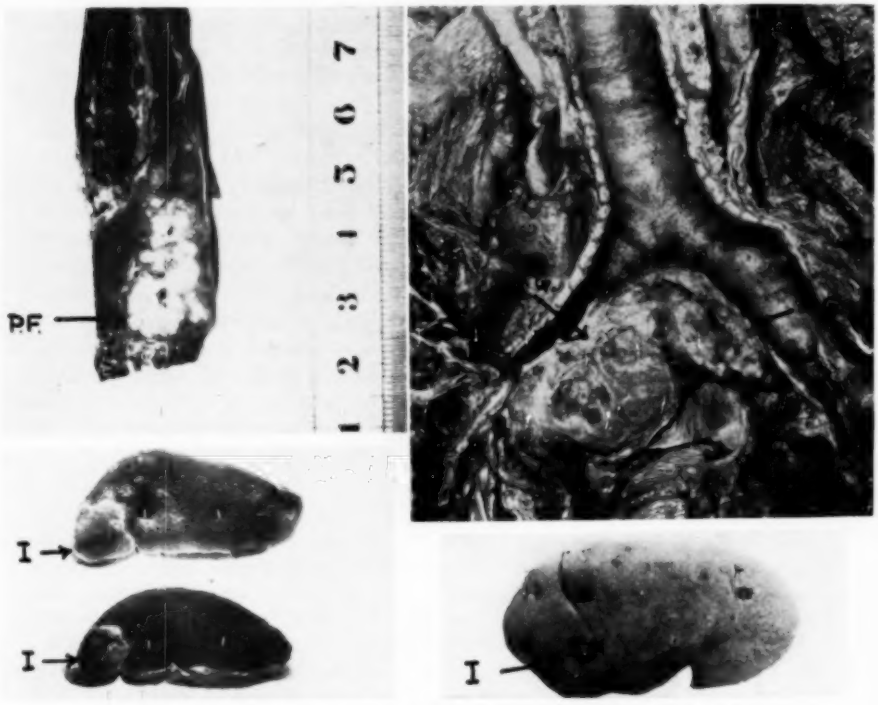

Fig. 1. (Upper left) (P.F.) Primary focus in the right lower lobe
Fig. 2. (Upper right) (P.G.) Confluent necrosis of the bifurcation lymph nodes, *i. e.* complementary primary lesion of the corresponding lymph nodes.
Fig. 3. (Lower left) Spleen with partly hemorrhagic infarction near the upper pole
Fig. 4. (Lower right) Kidney with small anemic infarct with hemorrhagic halo

zone (figure 3). There was a one-half centimeter in diameter anemic infarct with hemorrhagic halo (figure 4) towards the lower pole of the right kidney. There were raspberry-colored areas in the marrow of the femur while that of the sternum was a deep red.

Bacteriological investigations of postmortem material: Examination of a stained film of material from a bifurcation lymph node revealed numerous acid-fast bacilli. Cultures of material from bifurcation lymph nodes and splenic parenchyma yielded luxuriant growths of *M. tuberculosis.* Subcutaneous inoculation of a saline suspension of approximately 0.25 Gm. of macerated bifurcation lymph node into two guinea pigs caused

generalised tuberculosis which was discovered when they were killed forty-two days later. A rabbit inoculated with 0.001 mg. culture intravenously is still alive five months after infection.

It was concluded that a *human* strain of *M. tuberculosis* was responsible.

Careful postmortem roentgenography failed to reveal any trace of calcification in the lungs.

Histopathologic findings: Microscopic examination of the lungs revealed a diffuse hemorrhagic bronchopneumonia with much inflammatory edema but few cells. The latter were chiefly present in the alveolar phagocytes, some of which were filled with cocci. Polymorphonuclear leukocytes were scarce. The hemorrhages were chiefly visible in the periphery of the exudative lesions. Perivascular mononuclear cell infiltration and invasion of the intima of medium sized arteries were both present. Examination of other pneumonic areas revealed fibrinoid necrosis with central collections of cocci and peripheral hemorrhage. There were thickening and edema of arteriolar walls with mononuclear cell infiltration of the periphery of the adventitia. No acid-fast bacilli were demonstrable in appropriately stained sections of the hemorrhagic lesions.

Examination of the subpleural wedge-shaped caseous area revealed confluent caseous bronchopneumonia which was ill defined and showed very little, if any, evidence of encapsulation. The lesion was surrounded by a few lymphocytes distributed in the immediately adjacent atelectatic aveoli. The process appeared to be rapid and destructive as evidenced by fragments of bronchial cartilage and traces of vascular walls which could be seen in the peripheral part of the caseous area. Not more than two giant cells were found per section in the periphery of the focus and no classical tubercles were observed. The caseous area contained many acid-fast bacilli. Shadowy outlines of the elastic fibers of the alveolar septa were still visible but were entirely destroyed in those areas where there was beginning liquefaction. This change occurred in small patches and caused the usually pink caseous ground substance to assume a bluish tint presumably as a result of loss of the fibrinoid component.

The bifurcation lymph node contained confluent ill defined patches of fibrinoid necrosis which consisted chiefly of round chromatin fragments.

The sternal marrow contained many cells, many acid-fast bacilli. No polymorphonuclear leukocytes were seen but many "plasma cells" were present. The marrow also contained fair numbers of immature red cells, an occasional eosinophile and other immature leukocytes and some megakaryocytes. In addition, there were a fair number of ill defined areas of fibrinoid necrosis containing many acid-fast bacilli (figure 5). These areas were surrounded by active bone marrow as described above and revealed no evidence that any attempt had been made to form zones of cellular demarcation (figure 6).

A very few small Malpighian corpuscles were visible in the spleen and the grossly hyperemic pulp dominated the picture. The pulp was moderately cellular and contained numerous reticulo-endothelial cells, especially in the sinuses. Some of these cells were full of hemosiderin (erythrophagia). In addition, scattered in the pulp, were small areas of fibrinoid necrosis with a moderate number of chromatin fragments, mostly round and rod shaped. These areas are ill defined, devoid of any attempt at demarcation and abound with acid-fast bacilli (figure 8). Finally, some vascular changes were noted, which consisted of a fibrinoid necrosis of the intima of the larger veins. These lesions contained numerous acid-fast bacilli (figure 7). The vascular changes were particularly prominent in and around the large, partly hemorrhagic, splenic infarct.

No acid-fast bacilli were discovered in the splenic tissue outside the small necrotic foci.

Multiple periportal as well as intralobular areas of fibinoid necrosis were present in the

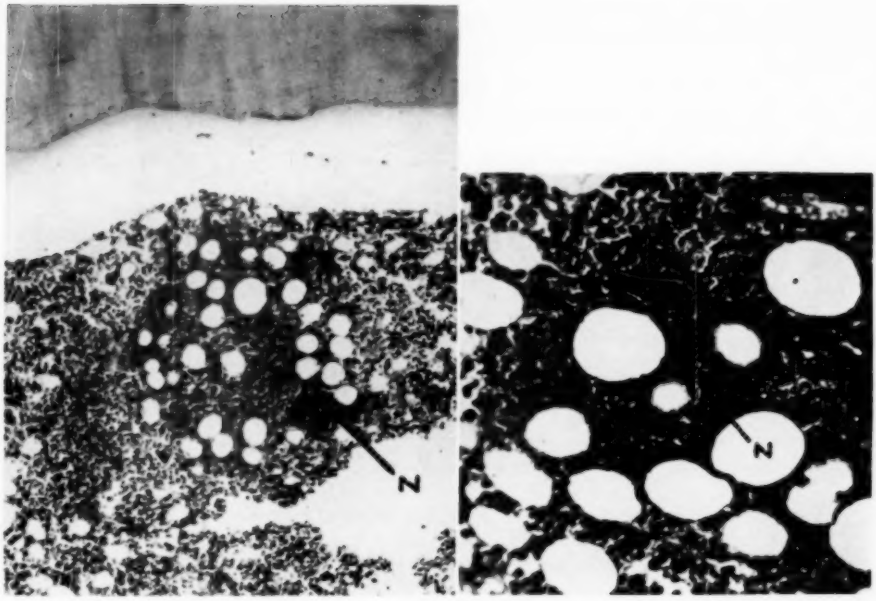

FIG. 5. (Left) Sternal marrow survey showing an area of fibrinoid necrosis (N) surrounded by collections of plasma cells mixed with scanty marrow cells. × 100.

FIG. 6. (Right) Close up view of area of fibrinoid necrosis (N) as shown in figure 5. Note plasma cells in the periphery of the necrotic area. × 300.

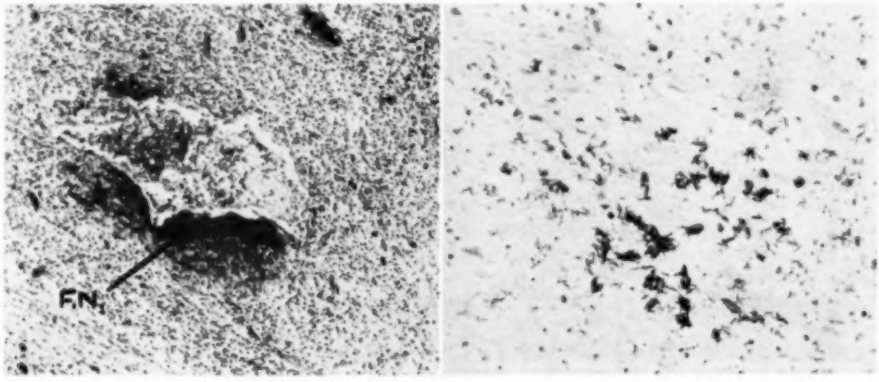

FIG. 7. (Left) Spleen: necrotising endophlebitis (F.N.) containing numerous tubercle bacilli (not shown). × 50.

FIG. 8. (Right) Spleen: from an area of necrosis. Ziehl Neelsen preparation. Mass of acid-fast bacilli. × 535.

liver. In the intralobular lesions proliferation of the Kupffer cells was prominent and many tubercle bacilli could be seen in the necrotic areas. There was an area of cortical necrosis in the kidney and the artery leading to the area was blocked by a thrombus. There were small areas of necrosis in the suprarenal cortex which contained moderate numbers of tubercle bacilli.

COMMENT

The wedge-shaped fresh caseous area in the lung, together with the wholesale necrosis of the bifurcation lymph nodes, constitute a primary complex, probably of short duration. Careful postmortem roentgenography of the lungs failed to show any trace of a preceding (now calcified) primary infection. It is therefore reasonable to conclude that the fresh lesion is of a primary nature in spite of the advanced age of the patient.

The process in this primary complex must have been rapid in view of the presence of "direct necrosis" rather than "caseation". The rapid nature of the necrosis is indicated by the predominance of *round* chromatin fragments, which originate from disintegrating lymphocytes and not from epithelioid cells, which leave long and bizarre nuclear remnants. The abundance of tubercle bacilli also points to a rapid process of tissue destruction.

Dissemination of tubercle bacilli, with resultant necroses, must have occurred from this primary lesion and corresponded to the five weeks of febrile illness. In spite of the microscopic areas of necrosis in the majority of organs, hardly any gross changes were visible. This is in contrast with the case previously reported from this hospital (1) and with the majority of cases recorded in the literature. Of the latter, only in the case reported by Scholz (2) were macroscopic changes not detectable.

The minimal gross changes in the present case included infarcts in the kidney and spleen. The former resulted from a nontuberculous arterial plug and the latter from tuberculous endophlebitis of one of the larger veins, the intima of which contained tubercle bacilli. A previous case reported by Pagel (3) was similar in that a large renal infarct and subserous petechiae were the only macroscopic findings.

Like the case previously reported from this service (1), the present case was characterised by a marked leukopenia attributable to the scarcity of leukocyte precursors in the marrow, and their replacement by plasma cells. Marked leukopenia (between 400 and 1,700 leukocytes per cu. mm.) has been described before, as a feature characteristic of tuberculous septicemia (2, 4, 5). In other cases, however, the total leukocyte count has been normal (6, 7, 8) or different blood changes were found, notably polycythemia (9), or acute myeloplastic leukemia with leukopenia (10). The case reported by Lenhartz (11) was one of a rapid miliary spread of only four weeks' clinical duration with the picture of acute myeloplastic leukemia. The similar observation by Crail (12), however, was chacterized by the long clinical course (about nine months) and splenectomy was performed.

The pulmonary portal of entry is consistent with a human tubercle bacillus infection, though it should be recalled that human bacilli have been recorded in

a number of cases of fulminant tuberculous septicemia in which the primary infection was abdominal. The latter cases seem more common than those following pulmonary infection. Only the cases described by Rennen (9), Balint (7), and Lenhartz (11), show evidence of a primary pulmonary infection.

SUMMARY

A case is reported of fulminant tuberculous septicemia of four weeks duration which was associated with a marked leukopenia. The portal of entry was a fresh pulmonary primary complex with direct necrosis, and tubercle bacilli of human type were isolated from the lesions. It is believed that this case belongs in the category of those rare cases in which virtually no gross changes are seen.

SUMARIO

Septicemia Tuberculosa Fulminante con Leucopenia

El caso comunicado es de septicemia tuberculosa fulminante de cuatro semanas de duración, asociada a hiperleucopenia. La vía de entrada fué un complejo pulmonar primario reciente con necrosis directa, aislándose de las lesiones bacilos tuberculosos de tipo humano.

Este caso corresponde a esa rara forma de infección tuberculosa en que el examen macroscópico apenas revela patología.

ACKNOWLEDGMENT

The authors wish to acknowledge their indebtedness to Dr. H. Joules for the clinical notes and discussions of the clinico-pathological aspects of the case, to Drs. J. D. A. Gray and E. Nassau and Mr. G. R. Bertram for assistance with the typing of bacillary strains, to Dr. G. Discombe for his opinion on the hematological aspects, and to Mr. L. G. Spain and Miss Beryl V. Buckle for technical assistance.

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AGRANULOCYTOSIS DURING THE STREPTOMYCIN TREATMENT OF MILIARY TUBERCULOSIS

Report of a Case

DAVID D. FELD[1]

INTRODUCTION

Toxic reactions to streptomycin have been recorded by numerous observers, but very little reference has been made to any deleterious effects upon the hematopoietic system. In a recent report (1) on streptomycin toxicity by Farrington and his associates, it is stated under miscellaneous observations: "Leukopenia without granulocytopenia appeared in two subjects in conjunction with the appearance of a drug sensitivity reaction. In another subject, leukoepnia (2,000 to 3,000 cells per cu. mm.) developed during the second month of therapy. A relative granulocytopenia was also present for approximately sixty days but eventually disappeared." They were doubtful that this reaction was on a toxic basis because the patient was a radiologist who apparently always had a low total leucocyte count and he was also suffering from acute hematogenous tuberculosis.

In a report (2) to the Council on Pharmacy and Chemistry on the effects of streptomycin on tuberculosis in man over 900 treated cases collected from the Veterans Administration, the Army, and the Navy are considered and eight instances (.98 per cent) of blood dyscrasia appeared during treatment. Five of these consisted of a relatively mild leukopenia with neutropenia. There were three instances, however, of agranulocytosis which was definitely due to streptomycin. Although one of these 3 patients had generalized miliary tuberculosis, cessation of streptomycin was followed by a return to normal bone marrow function despite progression of the disease.

The instances of leukopenia and granulocytopenia mentioned in these reports have not been presented in detail. Accordingly, it was thought advisable to report the following case in which leukopenia and agranulocytosis occurred, apparently as a complication of streptomycin therapy.

CASE REPORT

M. W., a 42 year old white male steelworker, was admitted to Muirdale Sanatorium on the evening of February 27, 1947.

His past history revealed that he had had rheumatic fever as a child. He was told that he had rheumatic heart disease, and he stated he had a "heart murmur as long as I can remember." For the six years prior to admission he had imbibed alcohol freely and on December 10, 1946, he had been admitted to the Milwaukee County General Hospital for acute alcoholism. A routine chest roentgenogram at that time was reported as being normal. He was discharged thirteen days later with a diagnosis of alcoholic psychosis. He returned to work and immediately began to notice dyspnea, loss of

[1] From Muirdale Sanatorium, Milwaukee County Tuberculosis Sanatorium, Milwaukee, Wisconsin, and Marquette School of Medicine, Milwaukee, Wisconsin.

appetite, weight and strength, chills and night sweats. He continued to work however, until February 18, 1947, at which time he developed a very severe epistaxis. He was admitted to a private hospital where the left nasopharynx was packed to control the bleeding. The pack was removed a number of times but had to be replaced because of persistent bleeding. A chest roentgenogram, obtained on February 27, 1947 because of persistently high temperature, revealed the characteristic findings of miliary tuberculosis and he was transferred to Muirdale Sanatorium.

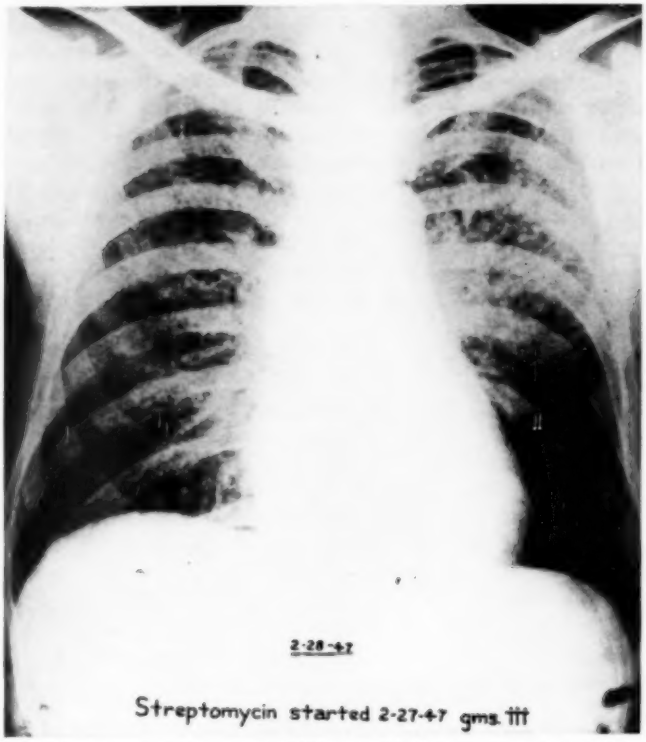

FIG. 1. Admission roentgenogram revealing a typical pulmonary miliary tuberculosis.

On admission to the sanatorium (February 27, 1947) his symptoms were similar to those that he had had at the onset of the disease, but were exaggerated. The temperature was 102.6°F. and the pulse and respiratory rates were 110 and 24 per minute, respectively. The physical examination revealed a fairly well developed and well nourished adult male (143 pounds) who appeared acutely ill. There was a nasal pack protruding from the left nostril which was dripping bright blood. The pack was removed three days after admission and no further bleeding occurred.

The significant findings upon examination of the chest were moist rales over the upper one-third anteriorly and posteriorly.

TABLE 1

DATE Streptomycin started 2-27-47	HEMOGLOBIN PER CENT	COLOR INDEX	RBC MILLIONS/CU.MM.	WBC PER CU.MM.	DIFFERENTIAL WBC (EXPRESSED IN PER CENT)							PLATELETS THOUSANDS/CU.MM.	N.P.N. γ PER CENT	REMARKS
					NEUTROPHILS	SEGMENTED	STAB	LYMPHOCYTES	MONOCYTES	EOSINOPHILS	BASOPHILS			
3- 1-47	71	.9	3.93	10,000	71	67	4	20	8	1				500 cc. citrated blood, March 3, 6, 10, and 24, 1947
3- 6-47	65	.93	3.56	7,050	77	69	8	16	4	1	2		29.5	
3-17-47	94	.98	4.88	7,850	57	55	2	22	15	6				
3-22-47	81	.92	4.46	3,100	26	23	3	53	19	0	2			
3-24-47				2,700	0	0	0	65	26	9				Neutrophils absent
3-25-47	Streptomycin stopped			2,250	1	1		50	39	9	1			Neutrophil degenerate
3-26-47				2,325	1		1	55	33	10	1			
3-27-47				2,375	1		1	62		6	2		51.2	
3-28-47				2,150	2		2	64	28	3	3			
3-29-47	87.7	.9	4.80	2,950	3		3	71	26			230		
3-31-47				2,825	19	11	8	52	29					
4- 1-47				2,800	20	7	13	49	28	3				
4- 2-47				3,950	38	19	21	37	22		1			
4- 3-47				5,300	57	34	23	28	15					
4- 4-47				7,350	58	38	20	29	13					
4- 5-47				10,450	67	48	19	20	13				40	
4- 7-47	87	.87	5.06	12,550	79	66	13	13	8					
4- 9-47				13,950	77	64	13	14	8		1			
4-11-47				17,150	77	61	16	12	11					
4-12-47	Streptomycin started			15,950	77	66	11	14	9				48	
4-14-47				12,250	74	59	15	15	9	2				
4-17-47	87	.85	5.19	12,400	73	65	8	13	8	6			38.4	
4-30-47				12,150	73	63	10	16	7	4			39.5	
5- 5-47	94	1	4.68	10,900	64	58	6	28	2	4	2			
5-12-47				9,450	66	60	6	22	10	2			44	
5-20-47				10,300	68	60	8	21	6	5			45.4	
5-28-47				14,900	81	73	8	13	3	3				maxillary antrum infection
5-31-47				10,800	76	73	3	16	12					
6- 7-47				10,500	59	52	2	16	15				51.9	
7- 2-47				9,350	55	51	4	27	12	6				
7-30-47				9,250	48	44	4	35	15	3			50	
8-21-47	94	.85	5.66	10,650	56	49	7	26	15	3			26.6	
9- 2-47				9,900	61	57	4	30						
9-25-47				10,200	57	52	5	36	7				31.9	
10-27-47				9,100	54	45	9	37	6	3				
11-27-47	100	1	6.24	9,250	61	50	11	33		2				
12-26-47	100	1	5.99	10,200	53	50	3	36	7	3	1		39.4	
1-29-48	107	.97	5.51	8,550	56	51	5	38	5	1				
3- 8-48	113	.97	5.86	9,000	56	54	2	38	4	2		308	29	

4- 2-47 Bone marrow biopsy—tubercle formation.
Streptomycin blood levels ranged from 2.5 to 5 γ per 100 cc.

Total days treated—250.
Total drug given—659.6 Gm.

There was a presystolic rumble and a harsh mitral systolic murmur over the apex and left sternal margin of the heart. The blood pressure was 110/60 in mm. of mercury.

The liver was not tender and extended 5 cm. below the costal margin. The spleen was not palpable.

The chest roentgenogram (figure 1) revealed the characteristic densities of miliary tuberculosis.

Examination of a concentrated specimen of sputum revealed acid-fast bacilli on microscopic examination. A Vollmer patch test for tuberculin sensitivity was positive.

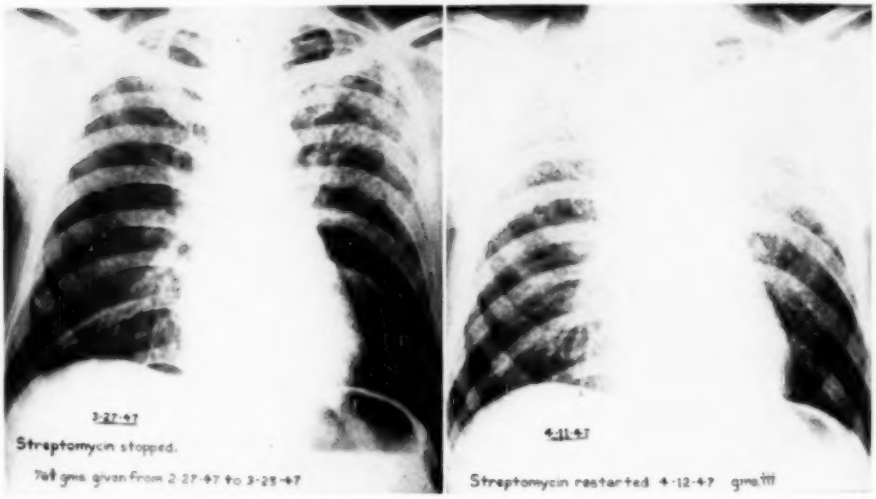

FIG. 2. (Left) Twenty-five days following the administration of streptomycin, leukopenia and agranulocytosis developed; nevertheless, slight clearing occurred in the lung fields and there was some improvement in the patient's general condition.

FIG. 3. (Right) Forty-three days after admission and sixteen days without streptomycin. Clinical condition is worse and there has been considerable increase in the pulmonary infiltration. However, the blood picture has definitely improved.

Therapy: Streptomycin therapy was started immediately and 3 Gm. were given every twenty-four hours, in divided doses at four hour intervals. The treatment was interrupted on the twenty-fifth day of March, 1947 because of leukopenia and agranulocytosis (table 1, figure 2). The total amount of drug which had been given was 76.6 Gm. Streptomycin from three different manufacturers was used during this period. At the time of the agranulocytosis the patient exhibited none of the other characteristic evidences of drug "hypersensitivity". Moreover, he denied ever having had episodes suggestive of allergic phenomena.

After a sixteen day interval, the daily dose of 3.0 Gm. of streptomycin was restarted April 12, 1947 and was continued until October 28, 1947, when it was reduced to 1.0 Gm. Streptomycin therapy was discontinued on November 23, 1947. The total number of days the patient was treated with streptomycin was 250 and the total amount of drug given was 659.6 Gm.

Other treatment consisted of: three blood transfusions of 500 cc. each of citrated blood given on March 6, 10, and 24, 1947; ferrous sulphate; and vitamin preparations. Two cc. of liver extract was given twice each week until April 21, 1947. The only other drugs given were Seconal, 0.09 Gm. (Sodium-propyl-methyl-carbinyl-allyl-barbiturate) from February 27, 1947 to March 30, 1947, a total of 1.5 Gm., and phenobarbital, 0.09 Gm. Since March 1947 there has been no other medication with the exception of an occasional dose of milk of magnesia.

Clinical course: The patient was very toxic and up to the time that streptomycin therapy was interrupted on the twenty-fifth day there had been no change in the temperature or pulse. There had been slight clinical improvement, however, and his appearance was better, his appetite had improved, and there was slight roentgenological improvement (figure 2).

During the sixteen day interval that the drug was withheld, the clinical condition of the patient grew worse, cough and expectoration increased and appetite decreased. A roentgenogram, taken at this time, revealed a definite increase in the pulmonary infiltration (figure 3).

In view of the patient's critical condition and the usually malignant nature of this type of tuberculosis, it was decided to reinstitute streptomycin therapy, using the previous dosage. Moreover, by the end of the sixteen day interval without chemotherapy, a high percentage of granulocytes were present in the peripheral blood (table 1). Streptomycin was reinstituted on April 12, 1947 and was followed by a gradual improvement in the patient's condition. On May 28, 1947 he developed an infection in the right antrum, associated with marked facial swelling and tenderness over this area. Penicillin therapy was started in addition to the streptomycin and within forty-eight hours the swelling and pain had completely disappeared. It should be noted that the added infection caused an appreciable elevation in the total leucocyte count with very little change in the percentage of granulocytes.

Improvement of the status of the tuberculosis continued, there was a weight gain of 30 pounds and during the six months after the cessation of streptomycin he had had no constitutional or local symptoms.[2]

The drug was given for a period, perhaps well beyond its benefits, but at that time experience in the streptomycin treatment of miliary tuberculosis was limited and the possibility of late relapse was well recognized.

In vitro studies of the streptomycin resistance of the patient's organisms could not be carried out as it was impossible to culture the tubercle bacilli. Obviously the infection was still very sensitive to the drug, however, even after twenty-five days of streptomycin treatment, as shown by the observed improvement when the drug was readministered.

Slight renal irritation, as indicated by occasional cylinduria, albuminuria and minimal azotemia were present, but disappeared completely after the cessation of chemotherapy. Very slight vestibular dysfunction was noticed for about the first three months of therapy, but numerous audiometric examinations revealed no abnormal findings.

COMMENT

Although miliary tuberculosis is recognized as being one of the etiological factors in leukopenia (3), the writer has never seen a case when leukopenia has been this marked or has been accompanied by neutropenia of the extreme degree noted in this patient.

[2] There has been no recurrence of the disease; patient remains in excellent condition.

In table 1 it should be noted that on March 24, 1947 and in four successive leucocyte counts, the neutrophils ranged from absent to one, one, two, and three cells, respectively. Eosinophils were always present, so the term agranulocytosis is in its strictest sense not correct. Nevertheless, the term has been used rather loosely (3) and can be applicable to this type of reaction.

Seconal (sodium propyl-methyl-carbinyl-allyl-barbiturate) and phenobarbital were given during the early phase of the disease. These drugs have never

FIG. 4. One year after admission, very slight apical fibroid residuals remain. No streptomycin therapy since November 23, 1947. Total days treated, 250. Total drug given, 659.6 Gm. Patient is in excellent clinical condition.

been implicated as a cause of leukopenia or agranulocytosis. Damachek (3) states: "The barbiturates have been suspected many times, but rarely has there been clear-cut proof of their relationship to the disease agranulocytosis."

During the phase of agranulocytosis, there was no decided clinical change in the patient's condition but as evil consequences were feared, administration of the streptomycin was stopped. Perhaps the patient became densensitized to the drug during the interim, although when the drug was re-established, a slight drop in the total leucocyte count from the preceding levels was noted. This might have indicated incomplete desensitization. Sherman (4) in discussing

drug allergy in relation to agranulocytosis states that in some patients in whom agranulocytosis or severe leukopenia has been attributed to sulfonamides (4a) or thiouracil (4b), the same drug has been subsequently tolerated without any reaction.

During the past five months, frequent total leucocyte counts (not all recorded) have been normal. The total leucocyte count has ranged from 8,500 to 10,000 cells per cu. mm. with normal percentages of the various cell types.

Studies of the bone marrow, unfortunately, were not satisfactory, but examination of a specimen obtained by bone marrow biopsy on April 2, 1947 revealed the presence of tubercle formation and hence confirmed the diagnosis of generalized miliary tuberculosis.

Although the initial sputum examination was positive for acid-fast bacilli on direct examination, the organisms failed to grow on culture. Numerous cultures of sputum and fasting gastric contents obtained subsequently have all been negative. The virtually normal roentgenographic findings one year after admission may be seen in figure 4. At the time of writing the patient is asymptomatic and fully ambulatory.

SUMMARY

A case of miliary tuberculosis in which leukopenia and agranulocytosis appeared during streptomycin therapy is reported. The total amount of drug given up to the time of the agranulocytosis was 76.6 Gm. within a period of twenty-five days. At the height of the reaction no neutrophils could be detected on one examination of the blood and in five successive examinations the total neutrophil percentages were: one, one, two, and three in that order. When streptomycin therapy was interrupted, the patient became worse, as evidenced by an increase in symptoms and pulmonary infiltration, but there was a return of circulating neutrophils. Streptomycin therapy was re-established after an interval of sixteen days in the same daily dose (3.0 Gm.) as was used before the agranulocytosis. No further toxicity was noted and there was gradual clinical improvement. The patient has been completely asymptomatic for six months following the cessation of therapy.

It is believed that the marked neutropenia represented a toxic reaction to streptomycin (presumably allergic in nature) and was not merely a consequence of the generalized hematogenous tuberculosis.

SUMARIO

Caso de Granulia con Leucopenia y Agranulocitosis

1. El caso comunicado es de un enfermo con granulia que manifestó leucopenia y agranulocitosis durante una reacción de hipersensibilidad a la estreptomicina.

2. La dosis total de estreptomicina para la fecha en que apareció la agranulocitosis era de 76.6 Gm., administrados durante un período de 25 días.

3. Al interrumpirse la estreptomicinoterapia, la agranulocitosis desapareció, pero la tuberculosis avanzó, según demostraron el aumento de los síntomas y la extensión de las infiltraciones pulmonares.

4. La estreptomicinoterapia fué reanudada al cabo de 16 días. No se observó más toxicidad y mejoró gradualmente el estado de la infección tuberculosa.

5. Una biopsia de la médula ósea reveló formación de tubérculos, indicando diseminación miliar generalizada de la infección.

6. El enfermo recibió un total de 659.6 Gm. de estreptomicina, administrados durante un período de 250 días.

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A DIRECT METHOD OF STANDARDIZING DILUTE SUSPENSIONS OF TUBERCLE BACILLI BY USE OF A CAPILLARY MICROPIPETTE[1]

WILLIAM D. CRANDALL

INTRODUCTION

The precision of methods used in standardizing bacterial suspensions has been limited by the difficulty of resolving two chief sources of error: (a) the irregular dispersion of bacteria in fluids or in direct smear preparations; (b) the variability involved in computing densities of the order of fifty thousand to one billion organisms per cc. on the basis of small numbers of organisms visualized in small fractions of a limited number of small aliquots of the suspension, *i.e.*, the "Microscope Factor" of Frost (1).

The following investigation was undertaken in an effort to point out the limitations of the present methods and to devise a method permitting more precise standardization of dilute bacterial suspensions (those containing less than fifty million cells per cc.) by reducing the above mentioned sources of error.

Bacterial suspensions are widely used as vaccines, in serologic reactions, and in the investigation of the properties of bacteria as regards growth, electrical potentials, et cetera. Although in practice concentrations of bacteria are measured indirectly by reference to dry or moist weight (2), volume of centrifuged organisms (3), opacity (4 to 8), or density (9, 10), these methods in turn must be standardized by direct methods.

The chief direct methods are: colony counts of dilution plating, chamber counts, and counts of bacteria in stained smear preparations. Colony counts refer to viable cells. The minimal coefficient of variation of the dilution plating method has been postulated to be ±6.6 per cent (11). The main sources of error are well known (1, 12, 13). The wide range of variation in colony counts by plating methods in the case of the tubercle bacillus has been demonstrated by many investigators (6, 14 to 18).

Chamber counts to determine the concentration of tubercle bacilli were introduced in 1891 (19). Notable improvements in this method have been the use of a counting chamber with a well depth of 0.02 mm. by Mallory and Wright (20), the use of bacterial stains (20), the application of darkfield illumination (21), and finally the use of a chamber with a well depth of 0.01 mm. (22). Although Blumenberg (23) claimed an error of 1.2 per cent of the average count with a suspension of approximately 232 million organisms per cc., the error of this method has been considered to be between 5 and 10 per cent of the average count with suspensions of more than 50 million cells per cc. (7, 12, 20, 22), (table 1).

With suspensions of less than 50 million cells per cc. the error has been found to be about 50 per cent of the average count (12). This large degree of error is understandable in view of the fact that one optical field with the 0.02 mm. depth

[1] From the Department of Medicine, University of Chicago, Chicago, Illinois.

counting chamber represents one twenty-millionth of a cubic centimeter and theoretically would contain only 2.5 organisms if a suspension of 50 million cells per cc. were being examined. The law of small numbers (33) would require the counting of at least 50 such fields and even then the factor for computing the density of the suspension would be 400,000. Hence, the counting chamber is not applicable to the standardizing of dilute bacterial suspensions.

The limitations of standardizing suspensions of bacteria by counting stained organisms in smear preparations depend upon several well recognized factors (24). The errors inherent in sampling have led to the use of the 0.01 cc. delivery pipette (0.0101 ± 0.00008 cc.) in preference to the standard loop (0.0111 ± 0.0021 cc.) (24), or the dropping pipette (26 to 29) for accurate delivery of small

TABLE 1

Variations in counts by the counting chamber methods

	INVESTIGATOR		
	Wilson (12)	Blumenberg (23)	Steiner (22)
Depth of chamber	0.02 mm.	0.02 mm.	0.01 mm.
Optical field area	0.0025 mm.^{2}	0.000625 mm.^{2}	0.0025 mm.^{2}
Fraction of cc. in optical field area	$\frac{1}{20,000,000}$	$\frac{1}{80,000,000}$	$\frac{1}{40,000,000}$
Density of the suspension used	14,730 million cells per cm.^{3}	232 million cells per cm.^{3}	1,200 million cells per cm.^{3}
Average number of bacteria per field	700	2.67 to 2.9	28
Coefficient of variation of field counts	—	—	12 per cent (on basis of ten fields)
Coefficient of variation of counts and Number of fields on which count was based	3 to 5 per cent (120 fields)	1.2 to 2.3 per cent (50 fields)	6.4 per cent (10 fields)

volumes. Likewise, a dispersal area of 1 sq. cm. has been accepted in preference to larger areas as the error in sampling diminishes as the sample approaches 100 per cent of the whole. For example, one hundred samples of one thousand items are more truly representative than are ten samples. On the basis of time consumption, the upper limit of the area of a smear which it is practicable to count microscopically is about 0.06 sq. cm. (300 optical fields of 0.0002 sq. cm. each), requiring fifteen to twenty minutes. And as this area represents 6 per cent of the 1 sq. cm. smear but only 1.2 per cent of the 5 sq. cm. smear, it is more truly representative of the former smear than of the latter.

The error due to the variability of dispersion of bacteria in the dried smear (14, 25, 30) has recently been emphasized by Hanks and James (31). This variability, together with the requirements of large numbers of samples neces-

sary to attain reliable values when dealing with small numbers (32, 33), has no doubt prevented the stained smear counting method from attaining an acceptable degree of accuracy for anything except the roughest sort of an estimation. For example, if 0.1 cc. of a suspension of 33,333 tubercle bacilli per cc. was spread over a 5 sq. cm. area and an optical system with a field area of 0.015 mm.^{2} was employed so that 50 such fields represented 1/666 of the original 0.1 cc., then twenty counts of 50 fields each would yield total counts of from one to ten bacilli and would give a computed value of from 6,666 to 66,666 bacilli per cc. (32).

As examples of the degree of precision of the stained smear method, the following observations are of interest. Breed (24), using the 0.01 cc. volume spread over an area of 1 sq. cm. and counting 100 fields of 0.0003 sq. cm. each (1/3,000 of the sample), found a coefficient of variation of 59 per cent on counting 14 samples and of 49 per cent on counting 15 samples of a suspension containing 5,500 cells per cc. Duplicate counts on 3 suspensions containing 40 to 123 million cells per cc. showed coefficients of variation from 18 to 21 per cent.

Breed and Stocking (35), using similar preparations and counting the organisms in 200 fields of 0.00015 sq. cm. each (1/3,000 of the sample), found coefficients of variation of 10.5 to 17.3 per cent on counting 72 samples of each of 3 suspensions which contained from one to four million cells per cc. Duplicate counts on 35 suspensions with an average density of 250,000 cells per cc. showed a coefficient of variation of 1.2 per cent.

Nuttall (26) used a dropping burette to deliver drops of 0.006 to 0.01 cc. size onto a glass slide. He measured the number of optical fields across the stained drop preparation and computed the total number of fields. A count of 500 fields was then used to compute the density of the suspensions. With suspensions computed to contain 13 million to 3,400 million tubercle bacilli per cc. he found the difference of the count between two separate drops to be 0.7 to 10 per cent of the mean count.

It is to be noted that the Breed smear technique uses a microscopic factor of 3,000 which is decidedly less than the factor of 400,000 employed in the chamber counting method. Nuttall's method, by utilizing a smaller area of dispersal, together with counting of a much greater percentage of the sample, still further reduced the variability.

A means of circumventing the sampling errors involved in counting a limited number of fields in stained smears with irregularly distributed organisms was demonstrated by Ziesche (36) in 1907, who counted all of the stained organisms contained in the entire smear of droplets collected by exposing a glass plate in the field of a patient's cough.

Theoretically the advantages of the Breed smear and of Nuttall's technique could be combined by making a smear with 0.0003 cc. of a bacterial suspension. Such a smear would permit counting of all the organisms and thus would avoid the errors of irregular distribution and of microscopical sampling and would have a microscopic factor of 3,333. A pipette to deliver 7 cu. mm. with an error of less than 0.3 per cent was described by Linderstrom-Lang and Holter in 1931 (37) and a modification of this pipette permitting manipulation of volumes of 0.5 cu. mm. was presented by Claff (38) in 1947.

EXPERIMENTAL

Methods and Materials

With the advice and aid of W. L. Doyle and L. S. Sonkin, micropipettes were fashioned by pulling a very fine tip, without local constrictions, on short segments of capillary tube with a diameter of about 2.5 mm. and a uniform bore of about 0.24 mm. diameter. A strip of graph paper lined in millimeters was fastened on the back of each pipette. A short segment of mercury measured at various positions along the pipette demonstrated uniformity of the bore above the tapering tip. Comparison of the weight of 10 mercury specimens with the length of the bore which they had occupied determined that a 10 mm. length of the bore was equivalent to 0.475 cm. with a standard deviation of the mean of $\pm$ 0.002 mm.[3]. Eleven samples of twenty normal sulphuric acid corresponding to 5 mm. lengths of the capillary bore were delivered into small dishes and titrated with one-tenth normal sodium hydroxide by S. Black, using an unpublished microtitration method. These titrations showed 5 mm. length of bore to be equivalent to 0.2297 cm. with a standard deviation of the mean of $\pm$ 0.0036 mm.[3] delivered.

The apparatus for using the capillary micropipette is shown in figure 1. The micropipette (A) is held vertically by means of a one-hole rubber stopper and clamp (B) connected to a ring stand. A short section of stiff rubber tubing (C) connects the upper end of the pipette to one branch of a glass tube with two right angle branches (D) which also is supported by a clamp (E) attached to the ring stand. Compressed air from the laboratory line is passed through filter and wash bottles to remove dust and moisture and enters the glass tube (D) at (F). Continuous flow is allowed by connecting one of the branches of tube (D) to a glass tube which extends about 20 cm. beneath the surface of water in a bottle (G) fitted with a two-hole stopper. The air flow is regulated at the outlet of the laboratory line of compressed air and by a screw clamp (H) on a short piece of tubing connected to the free arm of a "Y" tube interposed in the pressure line. The maximum pressure obtainable in the system is regulated by the depth of water in the pressure bottle (G), and as it is in the range of 18 to 20 cm. of water, small-caliber, thin-walled, soft rubber tubing may be used for the connections. The rate of delivery from the capillary micropipette is controlled by varying the degree of closure of tube (I) which is attached to the remaining arm of tube (D) and has a mouth piece at its distal end.

Rinsing the pipette thirty times with the suspension to be studied and then filling to the zero mark is accomplished rapidly by pinching closed the two rubber tubes of the pressure system at (J) and alternately applying suction and pressure through the mouth piece tube (I). Similarly, the pipette is cleaned with concentrated nitric acid, distilled water, alcohol and ether, using a short rubber tube with a mouth piece.

For delivery, the pressure in the system is adjusted by means of the screw clamp at (H) and the depth of water in the pressure bottle (G), so that when the pipette tip is not in contact with a body of fluid or a surface, no movement of the fluid in the pipette occurs when the mouth piece tube (I) is pinched closed. When a surface is touched to the pipette tip, closure of the mouth piece tube causes the capillary micropipette to empty at the desired speed. A magnifying glass, held in position by a clamp attached to the ring stand, is used to visualize the meniscus.

Below the pipette a rack and pinion are used to raise a glass slide to contact the pipette tip. The surface of the slide must be perpendicular to the vertical axis of the orifice of the pipette tip and the contact not so firm as to prevent flow. For this purpose the slide may be placed across the upper end of the draw tube of a microscope, or a mechanical

stage can be modified and held in place by a clamp attached to the ring stand, permitting a fine making and breaking of the contact.

Droplets of suspensions containing 0.08 to 0.2 per cent formalin delivered upon glass slides coated with a thin film of serum (by distributing a small drop of 50 per cent serum in distilled water in the manner of making a blood smear) were found to form a distinct margin upon drying which clearly delineated the droplet area in the stained preparation under the microscope.

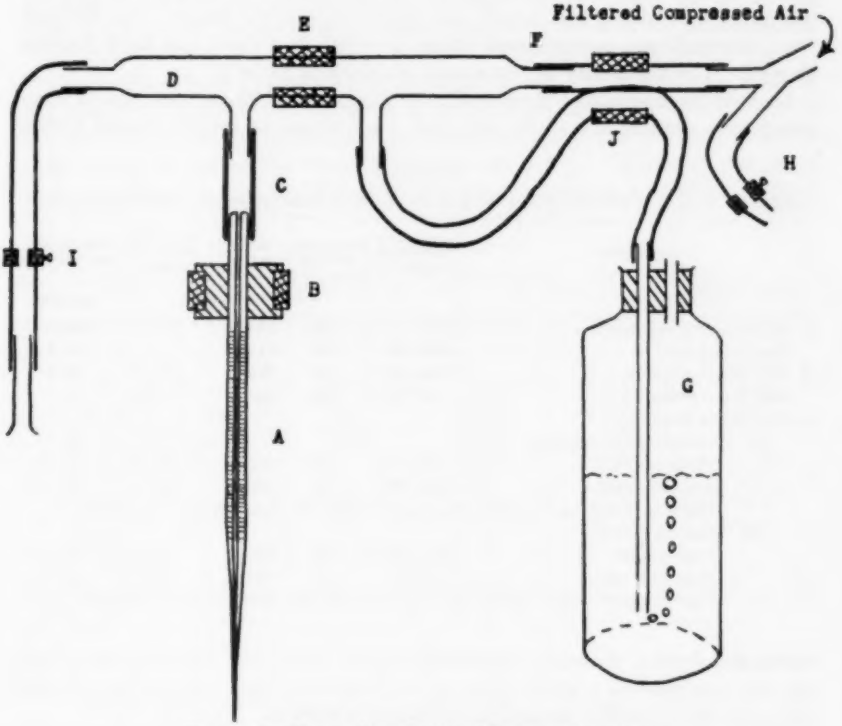

FIG. 1. Capillary micropipette with pressure system

Clump-free suspensions of tubercle bacilli containing only single cells were prepared by grinding a seven-day-old culture of H37-Rv in 0.2 per cent formalin, filtering through Whatmann # 42 filter paper twice, diluting to desired density and heating at 80°C. in a water bath for fifteen minutes. All suspensions were shaken mechanically for thirty minutes prior to use.

For counting, a Zeiss binocular microscope with 1.5× magnifying draw-tube prisms, achromatic 1.25 HI 90× oil immersion objective, and Abbe condensor was used. When counting pneumococci, 10× Huyghenian oculars were used (field area of 0.0094 mm.^{2}). When counting tubercle bacilli, 5× Huyghenian oculars were used (field area of 0.0276 mm.^{2}).

OBSERVATIONS

In order to determine the variability of aliquots from consecutive 5 mm. segments of the pipette as compared to the variability of aliquots delivered from the same segment of the pipette, a suspension of tubercle bacilli with a computed density of about 593,000 cells per cc. was used. Twelve aliquots of 0.23 cu. mm. size were delivered from consecutive segments of the pipette and twelve from the same segment of the pipette. It was noted that the former method was much more easily and rapidly accomplished than the latter. The droplets were delivered onto serum spread slides, air dried, heat fixed, and Ziehl-Neelsen stained. The variability of the counts is shown in table 2.

In order to determine the variability of aliquots of 0.23 cu. mm. size as compared with aliquots of 0.46 cu. mm. size, a suspension of tubercle bacilli with a

TABLE 2

Influence of mode of delivery, size of aliquot and error of counting on the variation of counts

EXPERIMENT	DENSITY OF SUSPENSION IN CELLS/CC.	NUMBER OF SAMPLES	MEAN COUNT	STANDARD DEVIATION OF MEAN (±)	COEFFICIENT OF VARIATION
					per cent
1. Consecutive segments	593,000	12	136.6	15.8	11.6
Single segment	593,000	12	149.5	21.5	14.4
2. 0.23 mm.³ aliquots	744,000	10	170.7	27.13	15.9
0.46 mm.³ aliquots	744,000	10	357.5	20.50	5.7
3. Duplicate counting:					
(a) Pneumococcus vaccine:					
First count	550,000	20	125.0	14.98	11.98
Second count	550,000	20	128.4	13.57	10.57
Error in counting = ±6.94 (5.48 per cent of the mean of the 40 counts)					
(b) Tubercle bacilli:					
First count	640,000	20	148.0	20.03	13.5
Second count	640,000	20	146.5	20.05	13.7
Error in counting = ±5.47 (3.71 per cent of the mean of the 40 counts)					

computed density of about 744,000 cells per cc. was used. Ten aliquots of 0.23 cu. mm. and ten aliquots of 0.46 cu. mm. size were studied. The larger aliquots showed a much smaller variability, as shown in table 2.

The error of counting was determined by the following procedures. Thirty-seven 0.23 cu. mm. aliquots of a pneumococcus vaccine, diluted 4,800 times in saline containing 0.15 per cent formalin, were delivered, air dried, gram stained and counted. The results showed a mean count of 126.5 organisms per aliquot with a standard deviation of ±15.16, *i.e.*, a coefficient of variation of 12 per cent. The density was computed to be about 550,000 cells per cc. in the diluted vaccine. Twenty of these aliquots were counted twice and the error of counting was determined as the square root of the sum of the squares of the differences between the duplicate counts divided by twice the number of pairs, *i.e.*, ±6.94 or 5.48 per cent of the mean of the forty counts (table 2).

Twenty 0.23 cu. mm. aliquots of a suspension of tubercle bacilli with a com-

puted density of about 640,000 cells per cc. were studied in like manner. The error in counting, estimated by the same procedure, was ±5.47 or 3.71 per cent of the mean of the forty counts (table 2).

A study was made of the range of variability as related to the density of the clump-free suspensions of tubercle bacilli in dilute formalin (0.08 to 0.2 per cent in distilled water). These counts were made on aliquots of 0.23 cu. mm. size and the densities were computed on the basis of the counts. As may be seen in table 3, very dilute suspensions with 75,000 tubercle bacilli per cc. or less showed a great variability in the bacterial content of the 0.23 cu. mm. aliquots. With suspensions containing from 350,000 to 850,000 tubercle bacilli per cc., the variability of the bacterial content was much less. In this range of density the maximum coefficient of variation of 15.9 per cent is much less than the 50 per cent error reported to be present with counting chamber determinations of suspensions containing less than 50 million cells per cc. Moreover, the range of the coefficient of variation from 8 to 16 per cent compares favorably with that

TABLE 3

Variation in counts as related to the density of the cell suspensions

DENSITY OF SUSPENSIONS IN CELLS/CC.	NUMBER OF 0.23 MM.^{3} SAMPLES	MEAN NO. CELLS PER 0.23 MM.^{3}	STANDARD DEVIATION OF MEAN (±)	COEFFICIENT OF VARIATION
				per cent
14,000 to 40,000	12	6.25	2.93	46.9
34,000 to 75,000	10	12.45	4.68	37.6
374,000 to 435,000	12	93.00	6.99	7.53
362,000 to 477,000	12	95.75	12.5	13.05
526,000 to 661,000	12	136.6	15.84	11.6
548,000 to 730,000	20	148.0	20.03	13.5
626,000 to 861,000	10	170.7	27.13	15.9

found in Breed-smear counts of suspensions with from one to four million cells per cc.

SUMMARY

1. The principal direct methods of standardizing bacterial suspensions have been briefly discussed in regard to their limitations and degrees of precision.

2. A modification of the Linderstrom-Lang pipette has been described together with details of its operation and a method of using it to make small smear preparations of bacterial suspensions.

3. Experiments with a capillary micropipette having a uniform bore throughout its working length of 6 cm. indicate that delivery of twelve aliquots through successive 5 mm. segments can be accomplished with much greater speed than can be obtained by refilling the pipette to the same place and delivering from the same 5 mm. segment each time. Moreover, this method of consecutive deliveries did not increase the variability of the bacterial counts on these aliquots.

4. By counting all the bacteria in a stained droplet smear of the bacterial suspension, the errors involved in counting limited numbers of fields in stained smears with irregularly distributed organisms are avoided. Total counts of the organisms in a smear of a 0.23 cu. mm. aliquot require fifteen to twenty minutes with the optical system used. A microscopic factor of only 4,348 is used to convert the count to organisms per cc. of the suspension. If aliquots of 0.46 cu. mm. are used, thirty to forty-five minutes are required for counting, but the microscopic factor is reduced to 2,174. By counting ten of the 0.23 cu. mm. aliquots, with three and one half hours counting time, the factor may be reduced to 435.

5. The error of counting the organisms in a 0.23 cu. mm. aliquot was found to be 5.48 per cent of the mean count with smears containing about 130 pneumococci each; and 3.71 per cent with smears containing about 150 tubercle bacilli each.

6. Preliminary experiments with this method indicate that the coefficient of variation of counts of suspensions of tubercle bacilli containing between 350,000 and 850,000 organisms per cc. is less (8 to 16 per cent) than with suspensions containing 75,000 or less organisms per cc. (38 to 47 per cent). Moreover, the coefficient of variation of these counts is less when aliquots of 0.46 cu. mm. are used (5.7 per cent) than when aliquots of 0.23 cu. mm. are used (15.9 per cent).

CONCLUSIONS

The direct microscopic counting of organisms in droplet-size stained smears of known small volumes of suspensions delivered by means of a capillary micropipette is presented as a method of standardizing dilute suspensions of bacteria.

The method may be compared favorably with existing methods as to simplicity, inexpensiveness, speed and precision.

Preliminary studies indicate that this method may be used to standardize dilute suspensions of bacteria with a precision at least equal to that of the Breed-smear technique and greater than that of the chamber-counting methods.

SUMARIO

Técnica Directa para Estandardizar por medio de una Micropipeta Capilar las Suspensiones Diluídas de Bacilos Tuberculosos

1. Analízanse sucintamente, con respecto a sus limitaciones y precisión, las principales técnicas directas para normalizar las suspensiones bacterianas.

2. Descríbese una modificación de la pipeta de Linderstrom-Lang, junto con pormenores relativos a su empleo y un método para usarla en la preparación de pequeños frotes de suspensiones bacterianas.

3. Los experimentos realizados con una micropipeta capilar de un calibre uniforme de 6 cm. en todo su largo efectivo indican que puede obtenerse la entrega de doce partes alícuotas a través de segmentos sucesivos de 5 mm. con una velocidad mucho mayor que la obtenible rellenando la pipeta hasta la misma marca y vertiendo cada vez del mismo segmento de 5 mm. Además, esta técnica

de entregas consecutivas no acrecentó la variabilidad de las numeraciones bacterianas en dichas partes alícuotas.

4. Contando todas las bacterias en un frote en gotilla teñido de la suspensión bacteriana, evítanse los errores derivados de la cuenta de cantidades limitadas de campos en fotes teñidos y en que los microbios están distribuídos desigualmente. En un frote de una parte alícuota de 0.23 mm.^{3}, la numeración total de los microbios consume de 15 a 20 minutos con el sistema óptico utilizado. Para convertir la numeración a gérmenes por cc. de suspensión, se emplea un factor microscópico de no más de 4,348. Si se usan alícuotas de 0.46 mm.^{3}, se necesitan de 30 a 45 minutos para la numeración, pero el factor microscópico desciende a 2,174, y contando 10 de las alícuotas de 0.23 mm.^{3}, con tres horas y media de numeración, puede bajar a 435.

5. El error cometido al contar los gérmenes en una parte alícuota de 0.23 mm.^{3} resultó ser 5.48 por ciento de la fórmula media en los frotes que contenían unos 130 neumococos cada uno; y 3.71 por ciento en los que contenían unos 150 bacilos tuberculosos cada uno.

6. Los experimentos preliminares verificados con esta técnica indican que el coeficiente de variación en las numeraciones es menor (8 a 16 por ciento) en las suspensiones que contienen entre 350,000 y 850,000 bacilos tuberculosos por cc. que en las que contienen 75,000 o menos por cc. (38 a 47 por ciento). Además, el coeficiente de variación es menor cuando se emplean partes alícuotas de 0.46 mm.^{3} (5.7 por ciento) que con alícuotas de 0.23 mm.^{3} (15.9 por ciento).

CONCLUSIONES

La numeración microscópica directa de los gérmenes en los frotes de tamaño de gotillas teñidos de pequeños volúmenes de suspensiones entregadas por medio de una micropipeta capilar se presenta como técnica apropiada para estandardizar las suspensiones diluídas de bacterias.

Esta técnica compárase favorablemente con las técnicas actuales en cuanto a sencillez, baratura, celeridad y precisión.

Los estudios preliminares indican que puede utilizarse esta técnica para normalizar suspensiones diluídas de bacterias con una precisión por lo menos igual a la técnica de frotes de Breed y mayor que la de las técnicas bacteriométricas.

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FACTORS AFFECTING THE SENSITIVITY IN VITRO OF TUBERCLE BACILLI TO STREPTOMYCIN[1,2,3]

ELIZABETH H. WILLISTON AND GUY P. YOUMANS

INTRODUCTION

The use of streptomycin as an adjunct in the treatment of tuberculosis and the emergence of strains of tubercle bacilli resistant to the drug in the patient raise the question of adequate laboratory tests for the detection of these resistant strains. The Dubos and Davis liquid Tween albumin medium (1) has been reported by Wolinsky and Steenken (2) as an "ideal one for determining streptomycin sensitivity of virulent human or bovine tubercle bacilli." Smith (3) has suggested that turbidimetric measurements in Tween albumin medium provide an accurate method for measuring growth of *M. tuberculosis* in the presence of streptomycin. Fisher (4), however, first called attention to the marked discrepancy between the sensitivity to streptomycin of tubercle bacilli tested in Tween albumin medium and the sensitivity of bacilli tested in the modified Proskauer and Beck medium enriched with serum, introduced by Youmans (5) and by Youmans and Karlson (6).

Fisher (7) found that Tween 80 alone was responsible for as much as a thousandfold increase in the inhibitory power of streptomycin for tubercle bacilli. Glycerol exerted a similar action but to a lesser degree. Fisher recommended that a test medium for streptomycin sensitivity should consist only of a liquid synthetic medium enriched with plasma or serum.

In view of the importance of detecting resistance to streptomycin of *M. tuberculosis* and the lack of unanimity as to method among workers in the field, the following studies were undertaken.

MATERIALS AND METHODS

The Tween albumin medium (1) as used by Steenken (8) has the following composition.

KH_2PO_4	1.00 Gm.
Na_2HPO_4—12 H_2O	6.25 Gm.
Sodium citrate—2 H_2O	1.50 Gm.
$MgSO_4$—7 H_2O	0.60 Gm.
Glucose	2.00 Gm.
Asparagin	2.00 Gm.
Distilled H_2O	1,000.00 ml.

pH 7.00

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[1] From the Department of Bacteriology, Northwestern University Medical School, Chicago, Illinois.

[2] Presented in part at the 44th Annual Meeting of the National Tuberculosis Association, New York, New York, June 16, 1948.

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These are autoclaved at 10 lbs. for 20 minutes before the addition of:

Vegex	0.2 Gm.
Tween 80	0.5 Gm.

The Vegex and the Tween 80 are autoclaved separately in 10.0 per cent aqueous solution at 10 lbs. for twenty minutes, and are added aseptically to the medium. Finally, bovine albumin (Fraction V) is mixed with saline to form a 10 per cent solution, inactivated at 55° for thirty minutes, sterilized by Berkefeld filtration, and then added aseptically to the above medium to give a final concentration of 0.2 per cent.

The serum-synthetic medium (6) (Modified Proskauer and Beck) is composed of the following ingredients:

Asparagin	5.0 Gm.
KH_2PO_4	5.0 Gm.
K_2SO_4	0.5 Gm.
Glycerol	20.0 Gm.
Distilled H_2O	1,000.0 ml.

The pH is adusted to 7.0 with 40 per cent sodium hydroxide and then magnesium citrate, 1.5 Gm., is added.

The solution is autoclaved at 15 lbs. for twenty minutes and sufficient filtered sterile serum (human, bovine, or horse) is added to make a final concentration of 10 per cent.

The two media were dispensed respectively in 100 or 200 ml. volumes to fourteen flasks where the appropriate amounts of streptomycin were added to all but one flask. The streptomycin (streptomycin hydrochloride) was dissolved in 0.01 molar phosphate buffer pH 7.0 and so added to make a final concentration in the flasks of media of: 1,000, 500, 100, 50, 25, 12.5, 6.25, 3.125, 1.56, 0.78, 0.39, 0.195, and 0.095 γ per ml. Finally, the media were dispensed in 5 cc. amounts to Pyrex test tubes (20 by 150 mm.) and capped with aluminum caps. These tubes could be kept in the refrigerator four or five weeks without loss of streptomycin potency.

The bovine alubmin (Fraction V) used throughout was obtained from Armour Laboratories (Lots C1403 and C1765).

Tween 80 (Lot 5669) was obtained from the Atlas Powder Company from a lot recommended for bacteriological use.

OBSERVATIONS

Comparison of Tween Albumin Medium With Serum-synthetic Medium

The sensitivity to streptomycin of the cultures of tubercle bacilli was determined by inoculating equal amounts of the cultures into the thirteen streptomycin concentrations and the control. The inocula used consisted of either 0.1 or 0.25 mg. wet weight of either a ground suspension or a seven day culture in Tween albumin medium. The same kind and amount of inoculum was employed in each case where comparisons were made. The tubes were incubated for twenty-eight days and examined at seven day intervals. The sensitivity to streptomycin of the culture was defined as the least amount of streptomycin which completely inhibited growth.

Most strains of *M. tuberculosis* grew so rapidly in both of the above media that readings could be made at the end of seven days. With some cultures, growth appeared upon further incubation in some of the concentrations of streptomycin in which growth had not been visible earlier.

In table 1 may be seen the sensitivity to streptomycin of 66 recently isolated strains of tubercle bacilli at the end of fourteen days of incubation. A twofold difference in sensitivity between strains was considered to be within the limits

TABLE 1

A comparison of the sensitivity to streptomycin of the 66 strains of tubercle bacilli on serum-synthetic medium and Tween albumin medium

	SENSITIVITY TO STREPTOMYCIN AFTER FOURTEEN DAYS OF INCUBATION*				
Strain Number	Serum-synthetic Medium	Tween Albumin Medium	Strain Number	Serum-synthetic Medium	Tween Albumin Medium
129	>1,000	>1,000	180	50	12.5
112	>1,000	>1,000	191	12.5	0.78
175	>1,000	>1,000	173	1.56	0.39
178	>1,000	50	176	6.25	0.78
195	>1,000	6.25	188	6.25	0.095
103	>1,000	>1,000	184	3.12	0.19
106	>1,000	>1,000	185	3.12	0.19
111R	>1,000	100	198	3.12	0.39
197	>1,000	>1,000	207	3.12	0.095
200	>1,000	>1,000	160	1.56	0.19
201	>1,000	>1,000	189	1.56	0.095
202	>1,000	>1,000	196	1.56	0.19
203	>1,000	>1,000	15	1.56	0.095
205	>1,000	>1,000	206	1.56	0.19
208	>1,000	>1,000	211	1.56	0.39
210	>1,000	>1,000	212	1.56	0.39
177	1,000	500	165	0.78	0.19
192	1,000	25	166	0.78	0.19
193	1,000	25	167	0.78	0.19
95	1,000	25	168	0.78	0.19
23R	1,000	50	169	0.78	0.19
187	100	3.125	170	0.78	0.19
194	500	25	171	0.78	0.19
58	500	25	172	0.78	0.19
73	500	12.5	174	0.78	0.19
128	500	25	186	0.78	0.095
24R	500	12.5	H37Rv	0.78	0.19
69R	500	25	6	0.78	0.095
100R	500	12.5	209	0.78	0.095
121	500	25	107	0.39	0.19
97R	500	6.25	182	0.39	0.19
204	500	12.5	183	1.56	0.19
213	500	50	190	0.39	0.095

* In γ per ml.

of error of the method. Fifty of the 66 cultures tested showed a resistance to streptomycin 4 to 160 times greater in the serum-synthetic medium than in the Tween albumin medium. Similar differences were observed after twenty-eight days of incubation. This discrepancy is similar to that reported by Fisher (4, 7)

and was attributed by him to the enhancement of the action of streptomycin by Tween 80.

Comparable streptomycin sensitivities in the two media were observed for 16 of the 66 strains. In both media, 13 of these 16 strains had a sensitivity to streptomycin greater than 1,000 γ per ml., the maximum amount of streptomycin used in the tests. If tubes had been used containing higher concentrations of streptomycin, it is possible that a discrepancy between the results of the streptomycin sensitivity tests with these organisms in the two media might have been revealed.

Before exploring the reason for the differences observed, however, it seemed advisable to investigate the role played by the size and type of inoculum employed in the tests.

Inoculum

The type of inoculum proposed (2) for streptomycin sensitivity tests in Tween albumin medium is a culture of tubercle bacilli grown in this medium for two seven day culture generations in order to ensure a well dispersed culture. The inoculum is then standardized by turbidimetric methods.

The inoculum originally proposed for the serum-synthetic medium is prepared by mechanically grinding the growth of tubercle bacilli obtained from solid media (6); determining the wet weight of cells per ml. by centrifugation in a Hopkins vaccine tube; and finally, diluting with 0.01 molar phosphate buffer to obtain the desired concentration of cells.

In the present study, the amount of growth in a seven day old culture of Tween albumin medium was also determined by centrifugation in Hopkins vaccine tubes. If this procedure indicated the presence of more tubercle bacilli than desired for any given test, the appropriate dilution was made with Tween albumin medium. If the culture had too few cells, it was incubated one or two days longer, and then restandardized.

The following tests were carried out to determine the effect of the nature of the inoculum, using 8 strains of tubercle bacilli, and of the amount of the inoculum, using 10 strains of tubercle bacilli.

Bacterial suspensions were prepared from Herrold's (9) egg yolk agar medium cultures and 0.25 mg. of each was suspended in 0.2 ml. of buffer solution. The suspensions were then delivered to each of the thirteen tubes of serum-synthetic medium forming the series of streptomycin concentrations, and to the controls. The Tween albumin cultures were standardized, and 0.25 mg. of these cells in 0.1 ml. Tween albumin medium was delivered to each of the thirteen tubes of serum-synthetic medium, and to the controls. After both sets of cultures had been incubated for fourteen days, the sensitivity to streptomycin obtained with the two types of inoculum was found to be the same. The tests were repeated with the same two types of inoculum, but with Tween albumin as the medium for the sensitivity test. In these tests also the streptomycin sensitivities were not affected by the kind of inoculum used. It should be mentioned that diffuse growth was obtained in the Tween albumin medium when a suspension prepared

by grinding was used as an inoculum as well as when suspensions obtained from growth in the Tween albumin medium were used as inocula.

Therefore, whatever ingredients might be responsible for the discrepancy previously observed between the streptomycin sensitivities in the two media, they do not occur in sufficient amount in the menstrua used for the inocula to affect the results.

One of the writers has previously reported (5) that within certain limits the size of the inoculum does not alter significantly the streptomycin sensitivity of the H37Rv strain in serum-synthetic medium. Further experiments on the effect of the size of inoculum were carried out as follows.

The inoculum was prepared from organisms grown in Tween albumin medium and separate tests were conducted with each of the 10 strains, using 0.25 mg., 0.1 mg. and 0.01 mg. of tubercle bacilli as inocula. Tween albumin and serum-synthetic media were inoculated.

With all strains, both the 0.25 mg. and 0.1 mg. inocula gave the same results in serum-synthetic medium. The results in Tween albumin medium using the above inocula were similar to each other although, as previously noted, they differed from those in serum-synthetic medium.

With an inoculum of 0.01 mg., however, the sensitivity to streptomycin of the cultures of tubercle bacilli was greater at fourteen days than with either the 0.25 mg. or the 0.1 mg. inoculum. After twenty-eight days of incubation, however, the streptomycin sensitivities were the same regardless of the size of the inoculum. This was true in both serum-synthetic and Tween albumin medium, except for a few strains which had a sensitivity to streptomycin greater than 1,000 γ per ml. These grew well in seven days in all tubes regardless of the size of the inoculum.

Within the limits set by the above experiments, the size or nature of the inoculum did not affect the sensitivity of tubercle bacilli to streptomycin.

Factors Responsible for the Discrepancy between Sensitivity of Tubercle Bacilli to Streptomycin in Tween Albumin and Serum-synthetic Media

Fisher (7) has reported that the discrepancy observed between the results of streptomycin sensitivity tests when carried out in Tween albumin medium and in serum-synthetic medium results primarily from the fact that Tween 80 increases the bacteriostatic effect of streptomycin. He also observed that glycerol had a similar action, but to a lesser degree.

As streptomycin assays of the two media using Romansky's method (10) showed that the streptomycin was not reduced in potency in either medium, the following studies were undertaken.

Six different modifications of the two media were prepared:

(S) Synthetic medium without glycerol or serum;
(SG) S + 2 per cent glycerol;
(SS) S + 10 per cent serum;
(SGS) S + 10 per cent serum + 2 per cent glycerol;
(DA) Dubos medium without Tween 80 but with 0.2 per cent albumin;
(DTA) DA + 0.05 per cent Tween 80

Eighteen strains of tubercle bacilli were used for testing the four modifications of the serum-synthetic medium. An inoculum (0.25 mg.) of each of the strains, prepared by grinding, was delivered respectively into tubes of each of the four media (S, SG, SS, SGS) containing the 13 concentrations of streptomycin previously employed. These tubes were incubated for twenty-eight days and examined every seven days.

In table 2 may be seen the sensitivity to streptomycin of each of these strains when grown for two weeks in the four modifications of the serum-synthetic medium.

TABLE 2

A comparison of the sensitivity to streptomycin of strains of human type tubercle bacilli when grown in various modifications of serum-synthetic medium and Tween albumin medium*

STRAIN NUMBER	TYPE OF MEDIUM					
	S	SG	SS	SGS	DA	DTA
165	0.39	0.39	0.78	0.78	0.78	0.19
173					3.125	0.39
H37Rv	0.78	1.56	1.56	1.56	1.56	0.39
H37RvR	>1,000.0	>1,000.0	>1,000.0	>1,000.0	>1,000.0	>1,000.0
200	50.0	1,000.0	1,000.0	1,000.0	500.0	1,000.0
204	25.0	100.0	500.0	500.0	500.0	50.0
207	0.78	0.39	3.125	6.25	1.56	0.39
192	500.0	1,000.0	1,000.0	1,000.0	500.0	50.0
178	500.0	500.0	1,000.0	1,000.0	1,000.0	50.0
196	N.G.	0.39	100.0	50.0	1.56	0.095
179	0.095	0.19	0.78	0.78		
182	0.19	0.39	0.78	1.56		
183	0.095	0.39	1.56	1.56		
209	0.095	0.095	0.39	0.39		
185	0.095	0.78	3.125	3.125		
167	0.095	0.39	0.78	0.78		
15	0.095	0.19	0.78	0.78		
188	N.G.	0.19	3.125	6.25		
212	N.G.	0.19	0.39	0.39		

N.G. = no growth in any tube.
* In γ per ml.

Effect of glycerol: Of the 18 strains tested, 10 after 14 days of incubation showed the same sensitivity to streptomycin in the basic synthetic medium with glycerol (SG) as in the medium without glycerol (S), (table 2). Five strains were more resistant in the presence of glycerol. No conclusions could be drawn concerning the 3 strains which failed to grow in fourteen days in the medium without glycerol.

The effect of glycerol in the presence of serum was determined by comparing the streptomycin sensitivities in the medium SGS with those in SS (table 2). The results were the same for all strains in both SGS and SS. Thus, the effect of glycerol alone, noted above, was not apparent in the presence of serum.

Effect of serum: The amount of growth of all strains in the control tubes was greater with serum than without. Three of the 18 strains did not grow in the basic synthetic medium without the serum after fourteen days of incubation. The effect of adding serum to the basic medium on the sensitivity of the remaining 15 strains to streptomycin may be seen by comparing SS with S in table 2. Ten strains were more resistant to streptomycin (4- to 32-fold) in the presence of serum. The remaining five gave similar results in the presence or absence of serum. The sensitivity to streptomycin of 10 strains was also decreased when serum was added to medium containing glycerol (SG compared with SGS, table 2).

Effect of Tween 80: Ten of the strains used for testing the ingredients of the serum-synthetic medium were also employed for the tests with the Tween albumin medium.

In table 2 may be seen the sensitivity to streptomycin of the ten strains in the Dubos medium plus albumin only (DA) and in the Dubos medium plus Tween and albumin (DTA).

The effect of Tween 80 on the inhibiting action of streptomycin is seen with 8 of the 10 strains and is lacking with only the 2 strains of a resistance greater than the streptomycin concentrations employed. The potentiation is from 4- to 20-fold with these particular strains. This is even more apparent if the results obtained with the 10 strains in SGS and DA are compared (table 2). With the exception of strain 196, the results in these two media are the same. Strain 196 did not give consistently similar results when sensitivity tests were repeated. This may be a reflection of the ease with which it produces streptomycin-resistant variants (11).

Although growth of the tubercle bacilli is frequently not as rapid, albumin can be used as a substitute for serum when preparing media for streptomycin sensitivity tests.

These results clearly confirm those of Fisher (7) that Tween 80 is the agent primarily responsible for the discrepancies observed between the results of streptomycin sensitivity tests in Tween albumin and serum-synthetic medium.

Effect of Amount of Tween 80 on the Bacteriostatic Action of Streptomycin

Batches of Tween albumin medium were prepared containing 0.05, 0.04, 0.03, 0.02, 0.01, 0.005, 0.003, 0.001 and 0.0005 per cent Tween 80, respectively, and streptomycin was incorporated in each in the same concentrations previously employed. Using 0.25 mg. of eight to ten day cultures of 6 strains of *M. tuberculosis* in Tween albumin medium as an inoculum, the nine series above were planted and incubated for fourteen days. As the inoculum itself was suspended in 0.1 ml. of 0.05 per cent Tween 80, the total Tween concentration in any one tube was increased by 0.001 per cent. Table 3 shows the sensitivity to streptomycin of the 6 strains grown in these media, and in serum-synthetic medium.

The cultures in the 0.05 per cent Tween 80 series of streptomycin dilutions were all well dispersed when the tubes were shaken after two weeks of incubation. In tubes with less Tween the degree of dispersion was less constant. For each

strain there was a critical concentration of Tween 80 below which the amount of dispersion observed in the Tween albumin medium containing 0.05 per cent Tween did not occur. The sensitivity to streptomycin also was not the same in all the concentrations of Tween 80. As the amount of Tween 80 was diminished, the sensitivity to streptomycin became progressively less. For each strain, however, there was a point where further decrease in the amount of Tween 80 produced no significant change in sensitivity to streptomycin. At this point, also, dispersion was no longer produced by the amount of Tween 80 present.

TABLE 3

The effect of the concentration of Tween 80 on the streptomycin sensitivity and dispersion of tubercle bacilli*

CULTURE NUMBER	SERUM MEDIUM	CONCENTRATION OF "TWEEN 80" IN PER CENT										
		0.051	0.041	0.031	0.021	0.011	0.006	0.005	0.004	0.002	0.0015	0.001
165		+			+	+	+	±	±	±	−	−
Streptomycin sensitivity	1.56	0.098			0.098	0.098	0.098	0.39	0.39	0.78	0.39	0.39
178		+	+	+	+	+	+	+	±	−	−	−
Streptomycin sensitivity	500	50.0	50.0	50.0	50.0	50.0	50.0	500.0	500.0	500.0	500.0	1000
196		+	+	+	+	+	+		+	±	−	−
Streptomycin sensitivity	3.12	0.095	0.19	0.19	0.19	0.19	0.19		0.39	0.39	0.78	0.78
187		+	+	+	+	+	+	+	+	±	±	−
Streptomycin sensitivity	100	1.56	1.56	1.56	3.12	6.25	6.25	50.0	50.0	50.0	50.0	50.0
204		+	+	+	+	+	+	+	+	−	−	−
Streptomycin sensitivity	500	25.0	25.0	25.0	25.0	25.0	50.0	50.0	100.0	100.0	100.0	100.0
173		+	+	+	+			+	+	±	−	−
Streptomycin sensitivity	1.56	0.095	0.095	0.19	0.19			0.39	0.39	0.39	0.78	0.78

+ = Dispersed growth
± = Partially dispersed growth
− = No dispersion
* In γ per ml.

Effect of Tween 80 on Nonacid-fast Organisms

In view of the fact that the previous tests indicated a relation between the degree of dispersion produced by Tween 80 and the potentiating effect on the bacteriostatic action of streptomycin, an investigation was undertaken to determine whether bacteria which do not owe their dispersal to Tween 80 would show an increase in sensitivity to streptomycin in the presence of Tween 80. Eleven strains of nonacid-fast bacteria were chosen which grew unclumped in broth. These were: 6 strains of *Staphyloccocus aureus*, 3 strains of *E. coli*, one of *E. typhi*, and one of *A. aerogenes*. Tubes of beef infusion broth containing streptomycin in concentrations varying from 40 γ per ml. to no γ per ml. (ten tubes) were prepared. A similar series was prepared, adding 0.05 per cent Tween

80 to the streptomycin broth. The inoculum for the streptomycin sensitivity tests with these organisms was 0.1 ml. of a 1 to 1 million dilution of a six hour culture of each strain. These streptomycin broths were inoculated with the test organisms, incubated, and inspected thereafter at twenty-four, forty-eight and seventy-two hours. The sensitivity to streptomycin of all strains was the same both in the presence and in the absence of Tween 80.

Modified Dubos Formula

McDermott and his associates (12) recommended the reduction of the Tween 80 to 0.02 per cent and the increase of albumin to 0.5 per cent in the Dubos formula to eliminate the potentiating effect of Tween 80. In the present studies this medium has been employed to test the sensitivity to streptomycin of 54 strains of tubercle bacilli, and the results were compared with those obtained in serum-synthetic medium. Of the 54 strains tested, 33 were four- to eightfold more resistant in the serum-synthetic media than in the modified Tween albumin medium. Of the 21 which gave essentially the same sensitivity in the two media, ten showed in both media a streptomycin sensitivity greater than 1,000 γ per ml. in both media. If the series had included concentrations of streptomycin greater than 1,000 γ per ml., it is possible that with these strains also a discrepancy between the results in the two media might have been revealed.

Dehydrated Media

Two other types of liquid media which were tested were those dispensed in dehydrated form (L14725 and L54720) by Difco. These media contained the salts as described by Dubos and Davis (1) plus proteose peptone No. 3, Bacto yeast extract and Bacto casitone. The only difference between the two media was that one (L14725) contained 0.05 per cent Tween 80. These Difco bases were dissolved in distilled water, and autoclaved in 90 cc. amounts. To this broth were added 10 cc. of sterile serum, containing 7.5 per cent dextrose, also supplied by Difco. Streptomycin sufficient to give the concentrations previously employed was added to the two media.

The sensitivity to streptomycin of 7 strains of tubercle bacilli was determined in the two Difco media and in serum-synthetic medium. The Difco medium, without Tween 80, gave results which were approximately the same as in the serum-synthetic medium. In the Difco medium containing Tween 80, however, there was a fourfold increase in the bacteriostatic action of streptomycin on 4 of the 7 strains tested.

Solid Media

Pyle (13) called attention to the fact that cultures of tubercle bacilli were not homogeneous with regard to their sensitivity to streptomycin. Using plates of Herrold's (9) glycerol egg agar medium containing different concentrations of streptomycin, she cultured *M. tuberculosis* from the sputum of patients who were to receive treatment with streptomycin. Pyle found that these cultures of tubercle bacilli were composed of cells which did not have a uniform sensitivity

to streptomycin. The same composite character existed in cultures taken during and after streptomycin treatment.

A sensitivity test that would give some indication of the relative numbers of streptomycin sensitive and resistant organisms in a culture would be of great value. Liquid media, however, are unsuitable for this purpose. A solid medium would permit an estimation of the relative amount of growth on the different concentrations of streptomycin. Moreover, such a medium might also be employed for the primary isolation and testing for sensitivity of tubercle bacilli to streptomycin in one process, thus reducing the time needed for the completion of the tests.

Herrold's Medium: Herrold's (9) glycerol-egg agar medium was prepared by autoclaving the nutrient agar base for thirty minutes in 150 ml. amounts and then adding a single egg yolk in a sterile manner after the agar had melted and been cooled to 50 C.

Basic agar:	Beef extract	3.0 Gm.
	Bacto Peptone	10.0 Gm.
	NaCl	50.0 Gm.
	Distilled H_2O	1,000.0 ml.
	Agar	15.0 Gm.
	Glycerol	60.0 ml.
	pH 7.2	

The appropriate amount of streptomycin was added to each flask just after the addition of the egg yolk. Twelve to fifteen ml. amounts were then converted into slants in screw-top test tubes and allowed to harden.

The inoculum for this series was prepared by growing cultures in Dubos medium for seven days, and then delivering 0.1 ml. (0.1 mg.) of this culture to each of the fourteen slants of Herrold's medium containing different concentrations of streptomycin. The inoculum was allowed to flow over the slants, which were then incubated in a horizontal position. At the end of seven days, the growth on the egg slant was not abundant enough to make accurate readings possible. After fourteen days of incubation, most strains showed profuse growth on the tube with no streptomycin and on some of the lower concentrations of streptomycin.

At this time (fourteen days) with streptomycin sensitive cultures, there was usually complete inhibition of growth in the higher concentrations of streptomycin. After four weeks of incubation, however, slight growth, consisting of one to several colonies, often appeared in one or two additional tubes containing concentrations of streptomycin two- to fourfold greater than the lowest concentration which had completely inhibited growth at fourteen days.

In table 4 may be seen the sensitivity to streptomycin of the 95 strains tested on Herrold's egg medium as compared with the results obtained with serum-synthetic liquid medium. Seventy-five of these strains (77.7 per cent) were found to be equally sensitive on both media at the end of two weeks, *i.e.* there was no more than a twofold difference in the results, the error inherent in the method. It should be noted, however, that this slight discrepancy was consistently in the

TABLE 4

Comparison of results of streptomycin sensitivity tests in serum-synthetic medium and Herrold's glycerol egg medium

	SENSITIVITY TO STREPTOMYCIN AFTER FOURTEEN DAYS OF INCUBATION*				
Strain Number	Serum-synthetic Medium	Herrold's Medium	Strain Number	Serum-synthetic Medium	Herrold's Medium
15	1.56	3.125	333	>1,000.0	>1,000.0
69R	100.0	100.0	334	25.0	25.0
129	500.0	>1,000.0	335	>1,000.0	>1,000.0
165	0.39	0.78	336	6.25	12.5
170	0.78	1.56	337	>1,000.0	>1,000.0
181	100.0	25.0	338	100.0	50.0
182	0.78	1.56	339	>1,000.0	>1,000.0
183	1.56	3.125	341	500.0	500.0
187	100.0	50.0	342	>1,000.0	>1,000.0
188	0.78	3.125	343	50.0	50.0
189	0.78	0.78	344	1.56	1.56
196	0.78	3.125	345	1.56	3.125
197	>1,000.0	>1,000.0	346	1.56	6.25
200	>1,000.0	>1,000.0	347	0.78	1.56
202	>1,000.0	>1,000.0	348	1.56	3.12
204	500.0	1,000.0	349	1.56	3.12
207	3.125	6.25	350	0.78	1.56
208	>1,000.0	>1,000.0	351	1.56	3.125
209	0.78	3.125	354	0.78	3.125
210	>1,000.0	>1,000.0	355	0.78	1.56
211	0.19	0.78	356	0.39	1.56
214	3.125	3.125	363	1.56	3.125
223	1.56	3.125	366	3.125	6.25
225	0.78	1.56	373	1.56	6.25
228	3.125	25.0	394	>1,000.0	>1,000.0
230	500.0	500.0	395	1.56	1.56
231	0.78	3.125	396	1.56	3.125
236A	500.0	500.0	398	6.25	6.25
244	0.78	1.56	399	1.56	3.125
245	25.0	25.0	402	3.125	6.25
247	100.0	1,000.0	403	500.0	500.0
249	12.5	12.5	404	12.5	25.
254	6.25	6.25	405	>1,000.0	>1,000.0
260	3.125	3.125	406	1.56	12.5
263	0.78	3.125	407	12.5	50.
269	3.125	3.125	408	500.0	500.0
273	.39	1.56	409	3.125	6.25
274	3.125	0.78	411	>1,000.0	>1,000.0
294	1.56	3.125	414	1.56	6.25
299	1.56	6.25	422	0.78	3.125
314	>1,000.0	>1,000.0	425	500.0	500.0
322	1.56	3.125	430	1.56	6.25
323	6.25	12.5	438	1.56	3.125
324	1.56	3.125	439	500.0	100.0
325	1.56	3.125	442	25.0	25.0
326	1.56	3.125	477	>1,000.0	>1,000.0
327	6.25	3.125	478	>1,000.0	>1,000.0
332	3.12	1.56			

* In γ per ml.

direction of a greater resistance on the egg slants. At the end of twenty-eight days of incubation, 78 strains (80.2 per cent) were found to be equally sensitive in the two media. Only 2 of the 95 strains, however, showed more than a four-fold difference in sensitivity on the two media at the end of four weeks of incubation.

Serum-synthetic agar medium: The addition of 1.5 per cent agar to serum-synthetic-streptomycin medium may also be used for determining streptomycin sensitivity. Fifteen strains were tested in this medium and the values obtained were compared with the results in serum-synthetic liquid medium. The results were the same in both media, but growth was somewhat slower in the agar medium.

A third solid medium was prepared by adding agar to the synthetic medium without the addition of serum. The tubercle bacilli grew very poorly, however, and readings could seldom be made until the tubes had been incubated four weeks.

Of the three solid media tested, the Herrold medium had the fewest disadvantages. The serum-synthetic agar required the addition of fresh serum, a tedious process. The synthetic broth plus agar was not sufficiently nutritious to provide enough growth to be read easily.

Detection of Small Numbers of Streptomycin Resistant Tubercle Bacilli

As the usefulness of a streptomycin sensitivity test may depend on the ability of the medium employed to detect the presence of a small number of resistant organisms in any culture isolated from a patient, the use of mixtures of sensitive and resistant organisms as inocula for streptomycin sensitivity tests was studied. H37Rv (streptomycin sensitive) and H37RvR (resistant to more than 1,000 γ of streptomycin per ml.) were each grown in Dubos medium (0.05 per cent Tween) for one week, at which time 0.1 ml. of each culture contained approximately 0.1 mg. wet weight of the bacterial cells. The cultures were shaken to give the maximum degree of dispersion. The resistant culture was diluted decimally with Tween albumin medium so that it could be combined in very small amounts with a fixed amount of the sensitive strain and used as inocula for streptomycin sensitivity tests.

In these mixed cultures it was observed that the amount and the time of appearance of growth in the concentrations of streptomycin which completely inhibited growth of streptomycin-sensitive tubercle bacilli was proportional to the number of resistant organisms in the mixture.

In table 5 may be seen the sensitivities to streptomycin of 6 such mixtures containing different relative numbers of sensitive and resistant organisms and grown in modified Tween albumin, in serum-synthetic and in Herrold's egg medium. As may be seen in the table, the presence of a very small number of resistant organisms in the inoculum influenced the results markedly. When as little as 0.001 per cent (10^{-6} mg.) of the total inoculum was resistant to streptomycin, growth occurred in all concentrations of streptomycin in all media.

The amount of growth in the tubes of Herrold's medium containing sufficient

streptomycin to inhibit growth of the sensitive organisms was, within certain limits, proportional to the number of streptomycin resistant organisms present. With 0.001 per cent (10^{-6} mg.) of streptomycin-resistant organisms in the mixture, only 2 to 11 colonies were present on each slant of Herrold's medium at the end of fourteen days. With larger numbers of resistant bacilli, the growth was more confluent but much less in amount than on the control medium. A difference could be detected in the amount of growth with as many as, but not more than, 1.0 per cent (10^{-3} mg.) of streptomycin-resistant tubercle bacilli in the mixture. These differences, however, tended to disappear as the time of incubation was extended beyond fourteen days.

In the liquid media these differences in the amount of growth were far more difficult to detect.

TABLE 5

Result of streptomycin sensitivity tests on mixtures of sensitive and resistant tubercle bacilli after 28 days of incubation

MG. INOCULUM		STREPTOMYCIN SENSITIVITY OF MIXTURE*		
H37Rv	H37RvR	Serum-synthetic Medium	Modified Tween Albumin Medium	Herrold's Egg Medium
0	10^{-1}	>1,000.0	>1,000.0	>1,000.0
10^{-1}	0	1.56	0.19	1.56
10^{-1}	10^{-2}	>1,000.0	>1,000.0	>1,000.0
10^{-1}	10^{-3}	>1,000.0	>1,000.0	>1,000.0
10^{-1}	10^{-4}	>1,000.0	>1,000.0	>1,000.0
10^{-1}	10^{-5}	>1,000.0	>1,000.0	>1,000.0
10^{-1}	10^{-6}	>1,000.0	>1,000.0	>1,000.0
10^{-1}	10^{-7}	1.56	0.19	1.56
10^{-1}	10^{-8}	1.56	0.19	

* In γ per ml.

The most important conclusion to be drawn from these experiments is that cultures of tubercle bacilli may contain very few resistant organisms but under the conditions of the *in vitro* sensitivity tests may appear to be entirely composed of resistant tubercle bacilli.

DISCUSSION

The results of the present studies show that the sensitivity of cultures of tubercle bacilli to streptomycin *in vitro* is partially dependent on the composition of the culture medium employed. It has been reported by other investigators, Alture-Werber and Loewe (14), Wallace, Rhymer, Gibson and Shattuck (15), Green and Waksman (16), Donnovick and Rake (17), Lenert and Hobby (18), Hobby and Lenert (19) and Berkman, Henry and Housewright (20), that the sensitivity to streptomycin *in vitro* of other species of bacteria is also influenced by the composition of the culture medium. A variety of substances, including glucose, peptones, and serum tend to reduce the bacteriostatic action of streptomycin. While the mode of action of these agents is not clear, they may inter-

fere in some manner with the bacteriostatic action of streptomycin. In the present experiments it is of interest that the two agents, glycerol and serum, which decreased the sensitivity of the tubercle bacilli to streptomycin, also stimulated the rate of growth. It should be pointed out that not all of the strains of tubercle bacilli employed showed a significant decrease in sensitivity to streptomycin in the presence of glycerol and serum, although growth was apparently stimulated. In a previous report (5) it was observed that the sensitivity of tubercle bacilli to streptomycin was not appreciably affected by the presence of serum in the medium. Only one strain (H37Rv) was tested in the presence of serum in that study and the streptomycin sensitivity of this strain is not significantly affected by serum.

Tween 80, on the other hand, as shown by Fisher (4), increased the bacteriostatic action of streptomycin for tubercle bacilli and this effect was proportional to the concentration of Tween 80 in the medium. Tween 80 has a similar potentiating effect on the tuberculostatic action of subtilin (21), chloromycetin, certain synthetic organic compounds (22) and penicillin (23). The mechanism whereby Tween 80 increases the bacteriostatic action of streptomycin is not apparent from the data of the present study. It appears to be related to the surface active properties of the compound and may, as proposed by Kirby and Dubos (23), permit a more intimate contact between the antibiotic and the bacterial cell. It is of interest that Tween 80 did not increase the bacteriostatic action of streptomycin for nonacid-fast organisms, nor was it bacteriostatic for these organisms as it has been shown to be for tubercle bacilli (24).

The variability in the sensitivity to streptomycin of tubercle bacilli under different conditions emphasizes the necessity for care in the selection of a medium for streptomycin sensitivity tests. The ideal medium would be one which duplicated precisely the conditions which obtain *in vivo*. The original Tween albumin medium containing 0.05 Tween 80 and 0.2 per cent bovine albumin would appear to be unsuitable because of the marked potentiation of the bacteriostatic action of streptomycin by this concentration of Tween 80. The modification used by McDermott *et al.* (12), and by Sadusk and Swift (25), in which the concentration of Tween 80 is reduced to 0.02 per cent and the bovine albumin is increased to 0.5 per cent, was more suitable as the increase in the bacteriostatic action of streptomycin is no more than four- to eightfold. The serum-synthetic, bovine albumin synthetic, and Difco dehydrated liquid media are free of Tween 80, and such of these media as contain serum possibly simulate more closely the conditions present *in vivo*.

All liquid media, however, possess other disadvantages. They do not readily permit the detection of streptomycin resistant variant cells (11), nor the determination of the relative numbers of streptomycin sensitive and resistant organisms present in a culture of tubercle bacilli. Furthermore, liquid media are not as suitable for the determination of the sensitivity of tubercle bacilli to streptomycin at the time of primary isolation from the patient.

A solid medium in which streptomycin could be incorporated would solve at least partially the above objections to the use of liquid media. Extensive use of

Herrold's glycerol egg medium for the determination of the sensitivity of cultures of tubercle bacilli to streptomycin has shown it to be useful for this purpose, and Pyle (13) has employed this medium for the determination of the sensitivity to streptomycin of tubercle bacilli directly at the time of primary isolation from sputum. Other solid media may be found which may be even more suitable.

SUMMARY

A variety of media, both liquid and solid, have been tested for their suitability for determining the sensitivity of cultures of tubercle bacilli to streptomycin. The effect of Tween 80, bovine serum, glycerol, and the amount of inoculum on the sensitivity of cultures of tubercle bacilli to streptomycin was also determined.

It was found that Tween 80, even in low concentration, increased the sensitivity of the majority of cultures to streptomycin. Serum (bovine) increased the rate of growth and decreased slightly the streptomycin sensitivity of some strains. Glycerol increased slightly the resistance of a few strains of tubercle bacilli to streptomycin. In the presence of serum, however, glycerol had no observable effect.

Within the limits tested (0.01 to 0.25 mg. wet weight) the amount of inoculum employed did not affect the sensitivity to streptomycin provided a minimum incubation period of twenty-eight days was used. Large inocula, 0.1 to 0.25 mg., permitted completion of tests within fourteen days.

The sensitivity to streptomycin tended to be slightly less on solid medium than on liquid serum-synthetic medium. Nevertheless, it was felt that a solid medium such as Herrold's glycerol egg yolk agar was satisfactory for such tests and possessed the additional advantage of supplying an approximation of the relative numbers of streptomycin resistant and sensitive tubercle bacilli.

SUMARIO

Factores que Afectan la Sensibilidad in Vitro de los Bacilos Tuberculosos a la Estreptomicina

Varios medios, tanto líquidos como sólidos, han sido comprobados en cuanto a su adaptabilidad para determinar la sensibilidad de los cultivos de bacilos tuberculosos a la estreptomicina. Tambien se determinó el efecto del "Tween 80," el suero bovino, el glicerol y la cantidad de inóculo sobre la sensibilidad de dichos cultivos a la estreptomicina.

Observóse que el "Tween 8," aun a concentraciones bajas, acrecentaba la sensibilidad la mayoría de los cultivos a la estreptomicina. El suero (bovino) acrecentó la velocidad del desarrollo y atenuó ligeramente la sensibilidad de algunas cepas a la estreptomicina. El glicerol realzó levemente la resistencia de unas pocas cepas a la estreptomicina, pero, en presencia de suero, no ejerció efecto observable.

Dentro de los límites ensayados (0.01 por 0.25 mg. de peso húmedo), la cantidad de inóculo empleada no afectó la sensibilidad a la estreptomicina, con tal que se usara un período mínimo de incubación de veintiocho días. Los inóculos grandes (0.1 a 0.25 mg.) permitían completar las preubas en término de catorce días.

La sensibilidad a la estreptomicina solió ser levemente menor con los medios sólidos que con los sero-sintéticos líquidos. Sin embargo, parece que un medio sólido, tal como el de agar-yema de huevo-glicerol de Herrold, resulta satisfactorio para dichas pruebas, poseyendo además la ventaja de revelar aproximadamente las proporciones relativas de bacilos tuberculosos resistentes y sensibles a la estreptomicina.

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THE

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Timetable of Tuberculosis.—Tuberculous infection in a person passes through a number of characteristic periods; in each of these periods a specific tuberculous condition appears frequently. The risk of falling ill with each specific type diminishes rapidly after the period characteristic of the condition. Stage 1 appears five to six weeks after the infection. It is characterized by tuberculin sensitivity, initial fever, erythema nodosum and the primary complex. There is nothing characteristic about the initial fever and only a tuberculin test indicates the true etiology of this, as well as of erythema nodosum. The sedimentation rate becomes elevated. Stage 2 occupies approximately the next three months. During this period, the malignant generalized forms of tuberculosis, particularly miliary and meningeal, occur. Sometimes, by means of special methods, tubercle bacilli may be cultured from the urine. Stage 3, the pleurisy period, follows immediately after Stage 2 and lasts about four months. The effusion is usually on the same side as the primary complex and is a hypersensitivity reaction. After this, the infection enters a latent stage which, in most people, lasts for the rest of their lives. In a minority, there is a fourth stage, which lasts about three years, until the primary complex is healed. This is the period of skeletal tuberculosis. Most cases appear during the first year, a large number during the second and the remainder during the third. In adolescents, this is also the period of pulmonary tuberculosis, most cases occurring within three years after the appearance of the primary infection. The age of the person is an important factor in determining the incidence of the conditions in the various stages.—*The timetable of tuberculosis, A. Wallgren, Tubercle, November, 1948, 29: 245.*—(*A. G. Cohen*)

Tuberculosis in Identical Twins.—Monozygotic twins, 22 years of age, had lived under identical conditions and had the same profession. One of the twins had a febrile episode during which roentgenograms revealed an infiltration in the apex of the right lung with a cavity in the right subclavicular area. Tubercle bacilli were found in the sputum. The other twin was examined as a contact and found to have an identical infiltrate with cavitation in the left lung; his sputum also contained tubercle bacilli. The parents had no roentgenographic evidence of chest disease but an older brother had had pulmonary tuberculosis treated by pneumothorax. After considering the problems of hereditary disposition to tuberculosis raised by these cases, the authors suggest that nurses with a family history of the disease be excluded from working on tuberculosis services. —*Sur les jumeaux tuberculeux, P. Braun & A. C. Maclouf, Rev. de la tuberc., 1947, 11: 707.*—(*V. Leites*)

Treatment of Tuberculous Glands.—The plan of treatment was to obtain healing and quiescence by medical means and then to remove the glands surgically. General measures included good food, rest, fresh air and ultraviolet light treatment. The patients usually remained ambulant. The head and neck were immobilized by means of a carapace. Fluctuant and cold abscess were in-

cised with a tenotomy knife; this usually did not lead to sinus formation. Enlarged tonsils were removed and attention was paid to the teeth. In addition, calciferol was given to 23 children and 11 adults. The first effect was a flareup which soon subsided. Of 14 children with draining sinuses, 3 were slow to respond; the others healed in one to three months. Of 6 adults with sinuses, 3 healed within three months and the other 3 more slowly. In every case, there was an increase in calcification and a definite decrease in periadenitis. The excised glands showed an acceleration of the normal healing processes. Before treatment, the red, white and differential blood counts, sedimentation rate, blood urea nitrogen and calcium and the renal function were determined. Toxicity of the drug was heralded by a rise in the blood urea, calcium and sedimentation rate. The daily dosage of calciferol for children was 100,000 units and for adults 150,000 units taken in tablet form. The total dosage reached 2 to 16 million units in children and 7 to 46 million in adults. Toxic symptoms of a mild degree were noted in 9 children and 2 adults, of a moderate degree in 2 children and one adult and severe in one adult. The earliest sign was constipation, followed by malaise, nausea, vomiting, anorexia, thirst and polyuria. There was no impairment of renal function in 11 patients and temporary impairment in 5. In one patient there was questionable permanent impairment.—*Calciferol in the treatment of tuberculous glands, S. Gauwain, Tubercle, November, 1948, 29: 259.*—(*A. G. Cohen*)

Diagnosis of Tuberculoderms.—(*1*) *Lupus vulgaris.* It occurs endemically in regions which have a moist, cool climate with relatively few hours of sunlight per year. It frequently begins in childhood and progresses very slowly. The first lesion is the so-called lupus nodule. It is a small, well circumscribed, red or brown infiltrate which cannot be obliterated by pressure. Later it has an apple jelly color, is covered by scales and may become fungoid in character. The histological picture is that of a tuberculous granuloma, occasionally with a central area of necrosis. *Lupus vulgaris* may appear on any part of the body but the face is an area of predilection. (*2*) *Lupus miliaris disseminatus.* This is a rare disease of sudden onset. The lesion consists of many discrete, noncoalescent, lupus-like nodules which appear within a period of six weeks. The nodules remain from three to six months and on healing leave a variola-like scar. At no time is there scale formation. Tubercle bacilli are demonstrated only with great difficulty; the tuberculin test may or not be positive. The eruption occurs almost exclusively on the face. (*3*) *Tuberculosis verrucosa cutis.* This is an inoculation tuberculosis usually encountered on the hands of physicians, veterinarians or butchers. The lesion is bluish red in color and forms scales early. The degree of verrucosity varies a great deal. There is always hyperkeratosis while caseation is absent. (*4*) *Tuberculids.* All tuberculids are probably hematoembolic processes. They are papular lesions, varying in size and secondary changes. The microscopic picture varies depending on the specific tissue response and the degree of secondary changes. The onset of this lesion is rather sudden. It usually has a self-limited course with a fairly rapid evolution.—*Criteria for the diagnosis of certain tuberculoderms, H. E. Michelson, J. A. M. A., November 6, 1948, 138: 721.*—(*H. Abeles*)

Gastric Tuberculosis.—Tuberculosis of the stomach is rare. Broders classifies the condition into (*1*) miliary tubercles of the stomach, (*2*) solitary tubercle, (*3*) tuberculous ulcer, and (*4*) pyloric stenosing tuberculosis. The author reports a case with miliary tubercles, ulcers and stenosis. The patient had epigastric pain, bloating, sour erustations and bouts of emesis. The stomach was resected and the patient died. At autopsy the lungs were free of tuberculosis. The stomach, duodenum and omental lymph nodes showed tuberculosis.—*Gastric tuberculosis, H. R. Morris, Am. J. Roentgenol., May, 1948, 59: 682.*—(*J. E. Farber*)

Tuberculosis of Stomach and Duodenum.—Two cases of tuberculosis of the stomach and one of the duodenum are reported. None of the patients had active pulmonary tuberculosis but abdominal lymphadenitis was a prominent feature. All 3 cases developed perforations or fistulous tracts at the site of their lesions. Roentgenologically there are no pathognomonic findings so that the ulcerative and infiltrative lesions can be confused with benign ulcer or carcinoma. The simultaneous involvement of the stomach and duodenum, the presence of fistulae or sinuses and signs of external pressure by enlarged lymph nodes are roentgenographic diagnostic findings suggesting tuberculosis even in the absence of any pulmonary lesion.—*Tuberculosis of the stomach and duodenum, H. W. Ostrum & W. Serber, Am. J. Roentgenol., September* 1948, *60: 315.*—(*J. E. Farber*)

Abscess after BCG Vaccination.—A 2 week old infant was vaccinated with BCG (0.04 mg.) in the right axilla by the subcutaneous method. He was transferred to another institution where his tuberculin test was found to be negative during the following three months. Revaccination was performed by scarification in the left axilla. One week later a small abscess developed at the site of the scarification and a few days later a similar abscess formed in the right axilla where the first dose of BCG had been given. Typical BCG cultures were obtained from both abscesses. The tuberculin reaction became positive shortly after the second vaccination. Thus, in this case bacilli had remained alive in the patient for three months without producing any clinical demonstrable local reaction and without rendering the tuberculin reaction positive.—*Petits abcès cutanés après revaccination par le BCG au siege d'une scarification récente et d'une injection sous-cutanée antérieure, J. Le Mellétier, Rev. de la tuberc., 1948, 12: 235.*—(*V. Leites*)

Seedbed of Tubercle Bacillus.—The necropsy records of Bellevue Hospital patients over 15 years of age were examined for the period from 1935 to 1944. The following conclusions are made: Among patients who died from tuberculosis the clinical diagnosis was incorrect six times more often for persons over 50 than for persons under 30 years of age. Among patients who died from other diseases but who harbored communicable tuberculosis, there was clinical recognition of the tuberculosis in only one-fourth. Older persons can have progressive disease with so few manifestations of illness that they may not seek the advice of a physician and may remain unrecognized sources of infection. The registration of death from tuberculosis in New York City appears to be below the actual death rate with respect to persons over 50 years of age. In a high proportion of new cases of tuberculosis in adults in New York City, the disease is apparently contracted from unrecognized sources of infection. Mortality rates do not indicate either the extent or the location of the seedbed in which the tubercle bacillus resides. The seedbed may be greater in extent today than it was twenty years ago, for it is largely concentrated in persons, principally men, over 45 years of age and these are more numerous today than they were a generation ago.—*Disregarded seedbed of the tubercle bacillus, E. M. Medlar, D. M. Spain, & R. W. Holliday, Arch. Int. Med., April, 1948, 81: 501.*—(*G. C. Leiner*)

Pneumopericardium.—Two cases of pneumopericardium are described; both occurred in the course of therapeutic pneumothorax. One patient had had a pneumothorax on the left for five days; the other on the right for six and a half months prior to the appearance of the pneumopericardium. Neither patient had symptoms and the diagnosis was made by fluoroscopy. The pathogenesis remains obscure although a free pleuropericardial communication is suggested as an explanation. Puncture of the pericardium by the pneumothorax needle is unlikely. The presence of pneumopericardium was not considered a contraindication for the continuation of pneumothorax.—*Le pneumopéricarde,*

complication rare au course de la pratique du pneumothorax therapeutique, J. P. Nico, J. Lacorne & R. Comsault, Rev. de la tuberc., 1948, 12: 48.—(V. Leites)

Activity of Pulmonary Tuberculosis.—It is important to make a rapid and accurate estimate of the activity of minimal tuberculous lesions found in mass surveys. More than 75 per cent of these lesions have acquired stability at the time they are found. Activity can be determined accurately by roentgenologic examination and more rapidly and economically than by bacteriologic methods. In a series of 699 such cases followed for two to five years, activity was correctly determined from the first roentgenogram in 86 per cent of cases. A large film and an experienced roentgenologist are necessary. The photofluorogram should be used for screening only. Patients with minimal inactive pulmonary tuberculosis should be followed with roentgenograms at three month intervals for two years after discovery and at longer intervals thereafter.—*Accuracy of roentgen determination of activity of minimal pulmonary tuberculosis, C. C. Birkelo & P. O. Rague, Am. J. Roentgenol., September, 1948, 60: 303.—(J. E. Farber)*

Cavities "Below the Diaphragm."—The authors report 3 patients under pneumoperitoneum therapy whose pulmonary cavities appeared to be below the diaphragm. The cavities were located in lung tissue below the dome of the diaphragm in the anterior and posterior sulci, thus producing the illusion described.—*Pulmonary cavities "below the diaphragm," P. Morganstern & I. Pine, Am. J. Roentgenol., May, 1948, 59: 677.—(J. E. Farber)*

Surgical Collapse Therapy in Children.—This is a statistical evaluation of the results of treatment of tuberculosis by surgical collapse in children five to fifteen years old from 1932 to 1947 in Passy, France. Until recently this was the only French tuberculosis center where surgery was used extensively in children. Of 146 operations, 64 were phrenic interruptions, 44 thoracoplasties, 33 extrapleural pneumothoraces, 4 Monaldi drainages, and one was a cavernostomy. Over the fifteen year period the indications have gradually changed. In 1932, 68 per cent of the operations were phrenic nerve paralyses, 23 per cent thoracoplasties, and 9 per cent were extrapleural pneumothoraces. In the course of 1947, 78 per cent of the patients were treated with extrapleural pneumothorax, 15 per cent with phrenic paralysis, and 7 per cent with thoracoplasty. Extrapleural pneumothorax at present is considered the best method in children, 83 per cent of the patients having a "complete result." However, a great number of the operations are admittedly of too recent date to be evaluated as to long term results. No patient has been made worse by the intervention. There was one death several years later due to contralateral spread. Thirty-one thoracoplasties were performed after abandonment of an ineffectual pneumothorax; only 39 per cent gave "complete results." Thoracoplasty on 3 patients, seven to eleven years old, produced no deformity of the thorax in contrast to patients eleven to fifteen years old in whom deformity was very marked. The present indications for temporary phrenic nerve paralysis with or without pneumoperitoneum are limited to basal lesions of recent date and central location.—*La collapsothérapie chirurgicale chez l'enfant tuberculeux de cinq a quinze ans, H. Joly, Rev. de la tuberc., 1948, 12: 310.—(V. Leites)*

Coccidioidomycotic Pulmonary Cavitation.—Humans become infected with *Coccidioides immitis* usually by inhaling the chlamydospores and arthrospores of the fungus. Symptoms develop, after an incubation period of one to three weeks, in about 40 per cent of infected men. In the remainder the disease is completely asymptomatic. Women have a greater frequency of erythema nodosum and, therefore, a larger proportion have clinically manifest disease. The pneumonic or respiratory symptoms are of varying severity.

Pulmonary cavitation may develop in an area of coccidioidal pneumonitis or in a residual lesion some months after the primary infection. The patients with cavities rarely have disseminated infections and apparently possess effective immune mechanisms. The frequency of cavitation in asymptomatic coccidioidomycosis is not known; the incidence in hospitalized cases in the United States Army has been 2 to 8 per cent. The coccidioidal etiology of 274 pulmonary cavities was verified by recovery of the fungus in 40 per cent, by serological tests in 49 per cent, and by a positive coccidioidin without a tuberculin reaction in 11 per cent. Concurrent tuberculous and coccidioidal infections were present in 7 of the patients. The coccidioidomycosis was not progressive in any of these and the tuberculosis was progressive in only one. The relatively benign nature of the cavities is indicated by the fact that in the military patients three-fifths of them were discovered incidentally. The initial roentgenograms were made on almost three-fifths of the civilian patients because of hemoptysis which, however, was rarely severe. The other signs and symptoms of tuberculosis were rare. Ninety per cent of the cavities were single and 70 per cent were located in the upper portions of the lungs. In diagnosing these lesions, the coccidioidin skin test was the first step. Approximately 10 per cent of the patients reacted only to coccidioidin stronger than 1:100; a few did not react to 1:10. When the serological test was negative and a tuberculin reaction occurred, the diagnosis could be established only by recovering the fungus from the sputum or gastric contents. In three-fifths of the patients with fungi in the sputum, the etiology could also be demonstrated serologically. When detectable in patients with cavities, complement-fixing antibodies were usually present in low titer in contrast to the high titer characteristic of disseminated infection. A decline in the antibody titer and a decrease in the sedimentation rate were noted while cavities were forming. Many cavities closed quickly but some remained open for years. Bed rest may have aided closure early but was of limited value later. The risk of dissemination has been negligible and the possibility of contagion remote so that drastic intervention should be reserved for specific indications. Phrenic interruption has closed some old cavities. Pneumothorax should not be used for peripheral cavities because of the hazard of creating a bronchopleural fistula. Surgical removal of a persistent subpleural cavity by lobectomy or wedge resection safely eliminates the danger of spontaneous hydropneumothorax, which occurred in 2.6 per cent of the cases presented. Coccidioidal cavities and spontaneous hydropneumothorax are much less hazardous than the corresponding tuberculous lesions and incomparably less dangerous than disseminated coccidioidal granuloma.—*Pathogenesis of coccidioidomycosis with special reference to pulmonary cavitation, C. E. Smith, R. R. Beard & M. T. Saito. Ann. Int. Med., October, 1948, 29: 623.*—(*E. A. Rouff*)

Pneumonia with Salmonellosis.—An outbreak of food poisoning due to *Salmonella montevideo* was observed in 350 persons. Of these, 19 patients (6 per cent) developed bronchopulmonary manifestations. Four patients had acute bronchitis. One patient had bilateral bronchopneumonia; *Salmonella montevideo* was found in his sputum. Fourteen patients had clinical and roentgenographic evidence of interstitial pneumonia. All of them had an initial acute gastroenteric phase, lasting two to eight days. In 8 of the 14 cases there was a quiescent interval of one to five days, followed by increased toxicity, fever and bronchopulmonary complaints. In 6 cases there was no quiescent interval. The bronchopulmonary manifestations lasted from four days to two weeks. Sputum was cultured one to three times in 8 cases without recovering *Salmonella*. Sulfaguanidine, given during the gastrointestinal phase in 8 patients, and sufadiazine, given during the pneumonic phase in 3 patients, were without effect.—*Pneumonia associated with acute salmonellosis, A. P. Ingegno, J. B. D'Albora, J. N. Edson*

& P. J. Janquinto, Arch. Int. Med., April, 1948, 81: 476.—(G. C. Leiner)

Asbestosis.—Forty case of asbestosis, autopsied at the Medical College of South Carolina since 1930, are reviewed. The disease apparently did not progress long after exposure to asbestos dust ceased, although the fibrosis persisted and finally became scar tissue. In the milder cases there was little to indicate any influence of the disease on the health of the patient and death was usually caused by some unrelated condition. In practically all of such cases the asbestosis was undiagnosed until necropsy. This was also true in most of the cases of moderate lung damage. Asbestosis was conspicuous only when advanced and even then it was not always the principal or sole factor in the terminal illness. Asbestosis bodies remained in the lung indefinitely and were found twenty-seven years after the last exposure to asbestos dust. The location of these bodies in the terminal bronchiole and in the vestibular area of the lobule is significant in the pathogenesis of the disease. Bodies of smaller size appeared in the peribronchial lymph nodes, where there was foreign body reaction but usually little fibrosis. The presence of asbestosis bodies in the sputum indicated only that there had been inhalation of asbestos and did not characterize the condition of the lungs. The bodies may be found for years after the last exposure, but they may not be present in the sputum even in advanced cases of asbestosis. Pleural involvement was not constant and was probably a secondary occurrence. Local, fibrotic, nodular lesions similar to those characteristic of silicosis occurred frequently, which suggests that they may have been produced also by the asbestos. Carcinoma of the lung was found in 7.5 per cent of the abestosis cases as compared with a general incidence of one per cent, suggesting that the two conditions are related. Tuberculosis of the lung was found more frequently than in general autopsy series but careful analysis fails to show any direct relationship.—*Asbestosis: Analysis of forty necropsied cases, K. M. Lynch & W. M. Connor, Dis. of Chest, November–December, 1948, 14.—(E. A. Rouff)*

Heart in Bronchial Asthma.—The cardiac and circulatory changes were studied in 301 patients with bronchial asthma. Physical examination revealed various degrees of emphysema in 61 per cent. Roentgenograms confirmed the frequency of so-called "drop-heart" with emphysema. It was present in 14 per cent of the patients without any auricular or ventricular enlargement. Although electrocardiography was often valuable, it was difficult to detect slight changes in the heart by this method. The most conspicuous electrocardiographic changes were (*1*) right axis deviation, (*2*) peaking and widening of the P waves in leads II and III, (*3*) depression of the ST segment with inversion of the T waves in leads II and III, (*4*) splitting of the R and S waves, and (*5*) prolongation of the QRS conduction time. Right axis deviation was present in 44 per cent of the cases, left axis deviation in 28 per cent, and no axis deviation in 28 per cent. Uncomplicated bronchial asthma did not change the cardiac configuration. Associated cardiac disease, pulmonary congestion, or structural deformity were responsible for enlargement of the pulmonary conus and arteries, as well as for right cardiac hypertrophy with electrocardiographic axis deviation. Any "aortic or mitral configuration" was a sequel to valvular heart disease and not the result of bronchial asthma.—*The heart in bronchial asthma, M. K. Hajos, Ann. Allergy, November–December, 1948, 6: 655.—(B. Hyde)*

Commercial Nebulizers.—The Council on Physical Medicine of the American Medical Association has accepted only 3 nebulizers now commercially available, the de Vilbiss Nos. 40 and 44 and the Holmspray No. 630. Physicians have recommended other designs but there is little information available about their characteristics. This study compares the performance of several nebulizers now being sold. Failure of the apparatus to per-

form satisfactorily was due to (*1*) the production of an insufficient amount of mist, (*2*) too many large particles which did not get beyond the mouth and pharynx, or (*3*) a preponderance of true vapor or of particles so small that they were exhaled. Nebulizers containing small amounts of distilled water were weighed before and after 500 compressions of the hand bulb, and the weight delivered by one compression was calculated. This weight varied in the different nebulizers from 13.0 to 0.4 mg. The "Breathing" nebulizer delivered the most mist followed in the order of decreasing delivery by "Asthma Neprin" and "Vaponefrin," "De Vilbiss No. 40," "Vapto," "Broemmel," "Peralta," "Felrodo," "Parke-Davis Nebulizer," "De Vilbiss No. 44," "Defender," "Stearns," "Parke-Davis Adrenalin Vaporizer." The "Breatheasy" discharged large droplets which lodged on the posterior pharyngeal wall. "Vapto" produced particles of a size reaching the upper respiratory tree and "Broemmel", a fine mist. "Parke-Davis Nebulizer," "Defender," and "Stearns" emitted droplets.—*A comparative study of commercial nebulizers, G. F. Harsh, Ann. Allergy, September-October, 1948, 6: 534.*—(*B. Hyde*)

"Nechaphyl" for Bronchial Asthma.—Thirty-five of 40 patients with bronchial asthma obtained relief from "nechaphyl with phenobarbital" which they judged to be at least as satisfactory as that obtained with various oral ephedrine preparations. No toxic manifestations were noted and "nervousness" was diminished. "Nechaphyl" alone was less satisfactory than oral ephedrine.—*Nechaphyl in bronchial asthma, S. W. Simon, Ann. Allergy, November-December, 1948, 6: 662.*—(*B. Hyde*)

Apical Lung Cancer.—Primary carcinoma of the lung located in the apex (Pancoast tumor) produces a characteristic clinical and roentgenographic picture. Clinically, the patient complains of shoulder girdle pain which later radiates down the inner side of the arm into the fourth and fifth fingers; the affected shoulder droops. The upper eyelid on the side of the lesion becomes ptotic and perspiration is absent over that side of the face and head (Horner's syndrome). Cough is generally absent. A mass can be palpated in the related supraclavicular area. Over the apex there is percussion dullness and diminished breath sounds. Roentgenograms reveal a well-defined homogeneous shadow of increased density high in the apex. The trachea is displaced and slightly indented. These tumors should be completely removed before extension to the mediastinum or brachial plexus has occurred. Radiation therapy has been disappointing but should be prescribed for all inoperable cases.—*Primary cancer of the lung with special reference to apical lung tumors, J. J. Stein, Am. J. Roentgenol., July, 1948, 60: 58.*—(*J. E. Farber*)

Mediastinal Cystic Hygroma.—Cervical hygromas are not rare. On the other hand, the literature contains reports of only 19 cases of cervicomediastinal and 8 of intrathoracic hygromas. To these, the authors add 3 cases of their own. The condition is a congenital malformation arising during the development of the lymphatics by budding. The mechanism whereby it appears in the chest is uncertain. Pathologically it is a thin-walled cystic structure lined by endothelium, and is usually multilocular. The fluid in it is thin. A variety of structures such as connective tissue strands, fat, blood vessels and nerves may be found within it. Clinically, hygromas of the neck are usually noted at birth; they do not cause symptoms unless they displace the trachea or esophagus. They are thin-walled and translucent. In the cervicomediastinal type, roentgenography shows a shadow in the upper chest on the side of the mass; this varies in size with crying and other activities. The mediastinal type is found only on routine roentgenologic examination and is difficult to diagnose precisely. Surgical excision is indicated for cosmetic reasons and to avoid infection or tracheal compression. The cervical portion is removed first. The intrathoracic portion is then sclerosed with

chemicals. — *Cervicomediastinal and mediastinal cystic hygromas, R. E. Gross & E. Hurwitt, Surg., Gynec. & Obst., November, 1948, 87: 599.—(A. G. Cohen)*

Traumatic Hemothorax.—World War II taught that prompt and repeated aspiration of traumatic hemothrax is the immediate treatment of choice. The purpose of this is to obviate the formation of adhesive fibrinous pleuritis. The latter may result in limitation of lung function or failure of re-expansion. Six exemplary cases are reported.—*Important sequelae and complications of hemothorax resulting from penetrating wounds of the pleural cavity, S. P. Barden, A. J. Roentgenol., April, 1948, 59: 525.—(J. E. Farber)*

Intrathoracic Injury.—Five per cent of 4,000 battle casualties admitted to one army hospital had wounds involving the intrathoracic structures. Roentgenograms should reveal (*1*) the presence and location of foreign bodies, (*2*) the extent of bony injuries to the ribs, spine and sternum, (*3*) lesions of the lungs, (*4*) lesions of mediastinal structures, and (*5*) the status of the pleura and the contents of the pleural space. Foreign bodies are frequently seen in the lung with little or no evidence of reaction in the lung or pleura. Many are arrested in the hilar and mediastinal structures. Traumatic lung lesions are usually small, circumscribed, and resolve uneventfully. Air and blood in the pleura are absorbed rapidly especially if promptly aspirated. Aspiration prevents thickened pleura and pleural infection. Mediastinal foreign bodies may escape detection and require overpenetrated films. Pericardial effusion suggests pericardial trauma.—*Roentgenological manifestations of intrathoracic injury due to missiles, W. A. Evans, Jr., Am. J. Roentgenol., May, 1948, 59: 662.—(J. E. Farber)*

Roentgenography of Hydatic Disease.—Closed hydatid cysts of the lungs differ roentgenographically from the open ones. The closed cyst, which usually does not contain daughter cysts, appears roengenographically as a round homogeneous shadow in the lung parenchyma. The intercostal spaces may bulge. As the cyst grows, it often loses its roundness and becomes polycyclic, being more often visible in lateral views. The sharp limits disappear due to a thickening of the pericystic membrane. Echinococcus causes displacement of the bronchi that surround the cyst but so do all benign tumors; bronchography is thus of little diagnostic help. Flurosocopy is also of little help, but the existence of large round shadows in both lungs is diagnostic of hydatid cyst. If a cyst bursts and the level of the liquid is visible, the roentgenographic diagnosis is assured. Pericystic emphysema after rupture of a cyst signifies death of the parasite. Clinically, this phase manifests itself by small hemoptyses. The sign of the double arch occurs only rarely after rupture of a cyst and is a hydropneumocyst with floating membrane. At times rupture of a cyst causes widespread inflammation and atelectasis of large areas of the lung. Some of these pneumocysts (or hydropneumocysts) disappear without treatment; others disappear following treatment including drugs, pneumothorax or surgery.—*Hydatid disease and its roentgen picture, P. M. Schlanger & H. Schlanger, Am, J. Roentgenol., September, 1948, 60: 331.—(J. E. Farber)*

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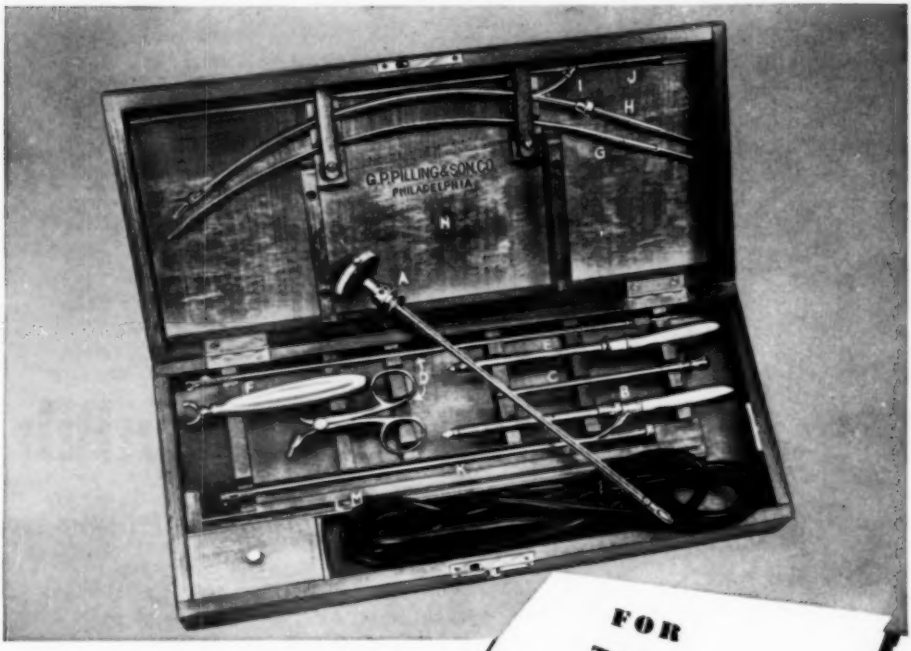

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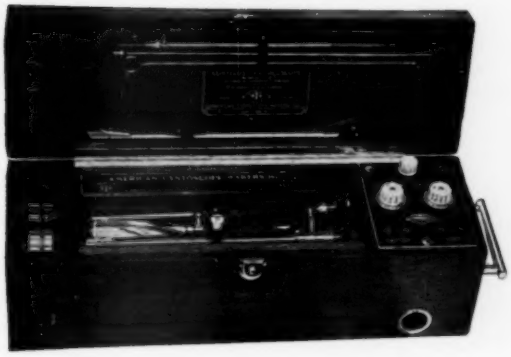

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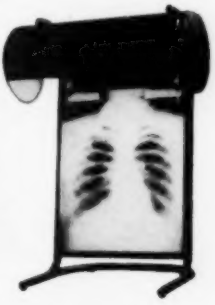

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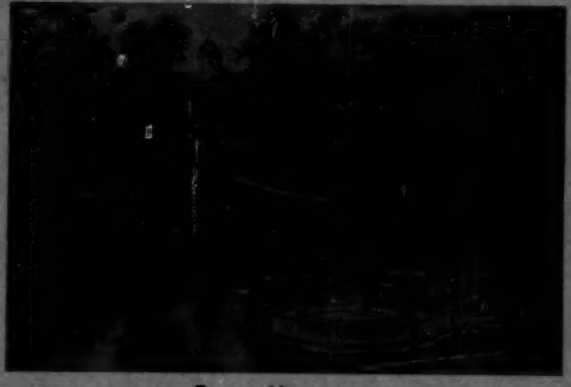

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